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POSTOPERATIVE VENOGRAPHIC CONTROL FOLLOWING LIGATION OF THE INFERIOR VENA CAVA

by

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Ligation of the inferior vena cava after COSSIO and PERIANES was performed in 30 decompensated cardiac patients. The clinical effect of the operation varied greatly; some advanced cases showed improvement, while others, the condition of which was not so serious, did not. It would appear likely that there are factors which are not caused by the clinical state but anatomic relations that are not nessarily the same in all patients. As we considered that one of the factors causing such a great difference in the effect of the ligation might be the type of collateral circulation, we performed postoperative venographies of the inferior vena cava in 5 of the cases.

The aim of these investigations was as follows:

1) To demonstrate the collateral circulation which develops after ligation of the inferior vena cava in decompensated cardiac patients.

2) To compare the various types of collateral circulation and the clinical effect of ligation, taking the speed of the circulation also into consideration.

3) To find out whether it is possible to draw prognostic conclusions from the type and speed of the collateral circulation.

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History

The inferior vena cava and its collaterals have for a long time been the subject of investigations by anatomists, pathologists, and clinicians. HALLER (1768) was probably the first, according to ROBINSON, to describe the collateral circulation in a case of obliteration of the lower third of the inferior vena cava found at autopsy. SAPPEY and DUMONTPALLIER (1862) injected tallow post mortem into the femoral and axillary veins to demonstrate the development of the collateral circulation after obliteration of the inferior vena cava. They reviewed the literature and described the different routes of the collateral circulation.

Different experimental studies, completed with roentgenography, were recently carried out in human cadavers. BATSON (1940) studied the function of the vertebral plexuses by injecting a contrast material into the dorsal vein of the penis in 100 cadavers. NORTHWAY and GREENWAY (1944) injected a suspension of red lead into the internal saphenous vein after double ligation of the inferior vena cava in its lower third. ROBINSON (1949) injected Neoprene into the internal saphenous or femoral veins of stillborn infants following ligation of the inferior vena cava in its lower part.

Experimental work in dogs, rabbits, cats, and monkeys was performed, inter alia, by PURPURA (1898), GOSSET and LECENE (1904), LEOTTA (1907), BEJAN and COHN (1911), BATSON (1940). These experiments demonstrated that ligation of the inferior vena cava, made below the renal veins, was well tolerated.

The first ligation of the inferior vena cava in man was performed by KOCHER in 1883 following operative trauma. At present this operation is performed rather frequently in patients with phlebothrombosis and thrombophlebitis in the lower extremities or pelvis to prevent the danger of pulmonary embolism. The same procedure was accomplished by COSSIO and PERIANES in decompensated cardiac patients. The first therapeutic results were described in 1948. In 1955 BERNATH et coll. published a report on 100 cases of vena cava inferior ligation in congestive heart failure.

The first roentgenologic demonstration of the inferior vena cava was described by DOS SANTOS in 1935. It seems that his method lay forgotten until 1947, when FARIÑAS and and O'LOUGHLIN separately published articles on the subject. ANDERSON (1951) demonstrated the vertebral venous plexuses roentgenologically by compressing the inferior vena cava. SURINGTON and JONAS (1952) by injecting the contrast medium into the internal saphenous vein demonstrated the collateral circulation in 3 patients in whom the inferior vena cava had been ligated 2 to $3^1/_2$ years previously in order to avoid danger of thromboembolism. NORDENSTRÖM (1955) studied the collateral circulation in dogs after the temporary occlusions of the inferior vena cava by introduction of a rubber balloon into the vein itself. HELANDER and LINDBOM (1955) studied the sacrolumbar circulation in 75 patients by compressing the inferior vena cava with a football bladder as used in urography and by injecting the contrast medium into both femoral veins.

Anatomic considerations

The inferior vena cava system is connected with the superior vena cava system by numerous anastomoses and many connections with the portal system also exist. (Fig. 1.)

When ligation of the inferior vena cava is performed in the region below the entrance of the renal veins, the main part of the circulation is effected through the vertebral venous plexuses and lumbar veins systems.

The system of the external and internal vertebral venous plexuses extends from the sacral region to the foramen magnum, and represents the network connecting the region of the inferior and superior venae cavae; it enables the circulation to be effected in the cranio-

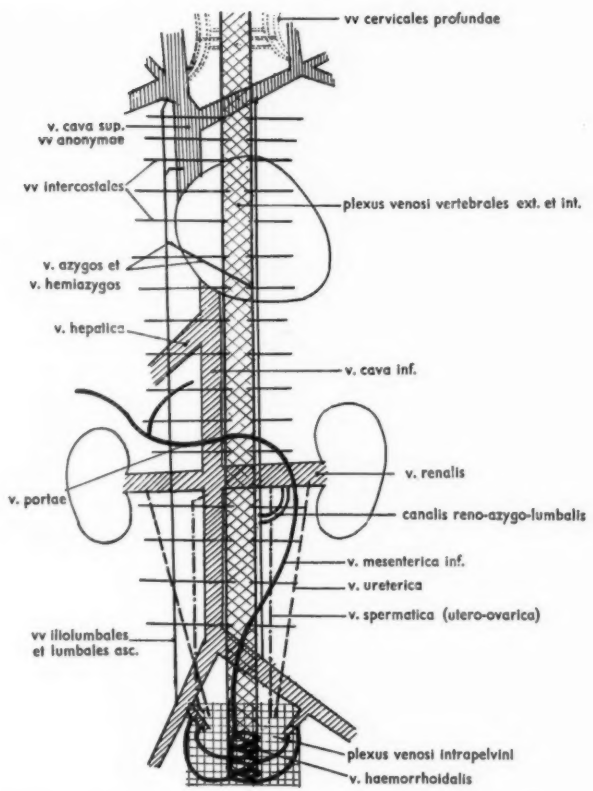


Fig. 1. Schematic drawing of the most important collateral routes and connections between the inferior and superior vena cava systems and vena portae, which start to function after ligation of the inferior vena cava.

caudal and caudocranial directions. This system is connected in the pelvic region with the inferior vena cava through the lateral sacral veins, which run into the hypogastric or common iliac vein, and through the middle sacral vein, which enters the left common iliac vein. In the lumbar region, the vertebral venous system communicates through the intervertebral veins with the lumbar veins, which empty into the inferior vena cava. It is connected with the azygos and hemiazygos systems through the ascending lumbar veins, joining the lumbar veins. In the thoracic region, the intercostal veins connect it with the azygos and hemiazygos veins, and in the cervical region it is drained by the vertebral and deep cervical veins.

The lumbar venous system is of particular importance in the collateral circulation. It begins with the lumbar branch of the iliolumbar vein which caudally enters either the hypogastric or the common iliac vein, and cranially continues into the lumbar ascending vein. This vein (by some authors called the lumbar azygos vein) connects the lumbar veins

and continues cranially into the azygos vein on the right side and into the hemiazygos vein on the left side, thus forming one of the three roots of these veins. In this way the systems of the inferior and superior venae cavae are connected.

In addition to this circulation along the vertebral plexuses, the blood of this system can circulate in a transverse direction through the lumbar veins into the vena cava, and in an ascending or descending vertical direction through the system — lumbar ascending or azygos and hemiazygos veins, respectively. Still more important is the fact that after ligation of the inferior vena cava blood can also reach the vertebral venous plexuses by the routes described, as all these systems have either no valves, or only insufficient ones, making circulation in both directions possible.

The system of the lumbar veins is also connected with the renal veins by the so-called reno-azygo-lumbar canal. This canal was found 62 times on the left and 6 times on the right side by LEJARS at 70 autopsies. It emerges from the posterior wall of the renal vein, proceeds caudally into the ascending lumbar and cranially into the hemiazygos and azygos vein, respectively.

Visceral anastomoses. The spermatic and utero-ovarian veins connect the pampiniform plexus on the left side with the left renal vein and on the right side with the inferior vena cava, respectively. The *ureteric* veins connect the region of the true pelvis with the renal veins. The venous plexuses in the true pelvis, which surround the urethra, prostate, urinary bladder, uterus, vagina and rectum and communicate with one another, connect the left with the right hypogastric vein into which they are mostly draining, but are at the same time joined with the external iliac vein and the portal system. In the event of obstruction of the inferior vena cava below the renal veins, the visceral anastomoses mentioned connect the regions of the external iliac and hypogastric veins with the regions of the inferior vena cava and renal veins, respectively, in a bridge-like manner. In such cases, they may attain the thickness of a finger.

The portal venous system is connected with the system of the inferior vena cava by a great number of anastomoses. The practical values of the collateral circulation in cases of ligation of the inferior vena cava seems to lie only in the superior haemorrhoidal vein. It proceeds cranially into the inferior mesenteric vein and caudally through the haemorrhoidal plexus with the middle haemorrhoidal vein which latter, after joining the prostatic, seminal and vaginal veins, leads into the hypogastric vein. It is also connected with the inferior haemorrhoidal vein, which empties into the internal pudendal vein. The other anastomoses, as for example the connection of the sacral veins with the haemorrhoidal plexuses, the peritoneal anastomoses (system of Retzius) between the peritoneal branches of the portal vein and the parietal branches of the sacral, lumbar and perirenal veins, and lastly the paraumbilical veins, are seldom of great significance.

The collateral circulation is possible even in cases in which the obstruction continues into the common and external iliac vein. In such cases the medial circumflex femoral vein starts functioning by uniting the femoral with the internal iliac vein through the obturator and inferior gluteal veins, thus enabling the circulation through the lumbar veins and vertebral venous plexuses system. If the femoral vein is also occluded, there are still the anastomoses between the internal saphenous vein and the spermatic or ovarian vein through the external pudendal vein and the superficial veins of the dorsum of the penis, respectively.

Of the least practical importance in obstruction of the inferior vena cava in its lower third are the communications with the deep and superficial veins of the abdomen, which through connections with the corresponding thoracic veins unite the inferior and superior vena cava systems. These anastomoses are by far more significant if the obstruction continues into both common iliac veins or even into the external iliac and femoral veins.

a b

Fig. 2. Female, aged 17. Five weeks after ligation of inferior vena cava. a) 3 sec after beginning of injection. Contrast medium already enters inferior vena cava above the ligation through the lumbar veins, internal and external vertebral venous plexuses, and the left renal vein; this latter communicates with the lumbar veins by the wide reno-azygo-lumbar canal. Shallow filling defect on right border of inferior vena cava marks the entrance of the right renal vein. b) 13 sec later. Both utero-ovarian veins are contrast filled (arrows). Strong reflux of contrast medium into the hepatic veins.

Material. Postoperative venography of the inferior vena cava was performed in 5 patients, 4 male and 1 female, the ages varying from 17 to 49 years. The venographies were carried out 5 to 15 weeks after the ligation. In 4 cases the clinical diagnosis was mitral disease with decompensation and pulmonary and hepatic stasis. In one case the ligation was performed for subchronic exudative polyserositis with adhesive pleuropericarditis and decompensation. The first venography was carried out in September, 1955. All the patients are still under control.

Method. In all cases 30 ml Joduron 50 % were simultaneously injected into both internal saphenous veins at a rate of 10 ml per sec. The patients were investigated in the supine position. Four examinations were made with an Elema film changer, and one with manual changing of the cassettes.

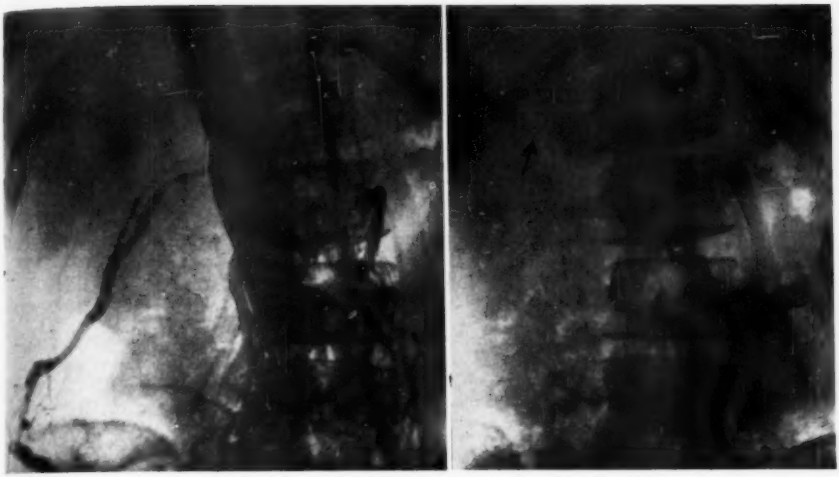
a b

Fig. 3. Male, aged 18. Six weeks after ligation of inferior vena cava. a) 4.5 sec after beginning of injection. Both common iliac veins are filled with contrast medium up to origin of inferior vena cava. Nearly all contrast medium empties into inferior vena cava above the point of ligation, partially through the lumbar veins and the internal and external vertebral venous plexuses, and partially through the reno-azygo-lumbar canal into the left renal vein. A small amount enters the azygos and hemi-azygos veins. Part of inferior vena cava between the ligation and the common iliac veins does not fill probably because of post-operative thrombosis. b) 8 sec later. Strong reflux of contrast medium into hepatic veins.

The intervals between the exposures were 0.5 sec in one case, 1 sec in two cases, and 2 and 3 sec respectively in another two. The duration of the serials was 14 to 21 sec. These venographies produced no untoward effects.

Results

The reno-azygo-lumbar canal was in two of the cases (Figs. 2a and 3a) found to be very important for the collateral circulation after ligation of the inferior vena cava, as it connected the lumbar veins system with the left renal vein. To our knowledge, this canal has not yet been demonstrated roentgenologically in living human subjects.



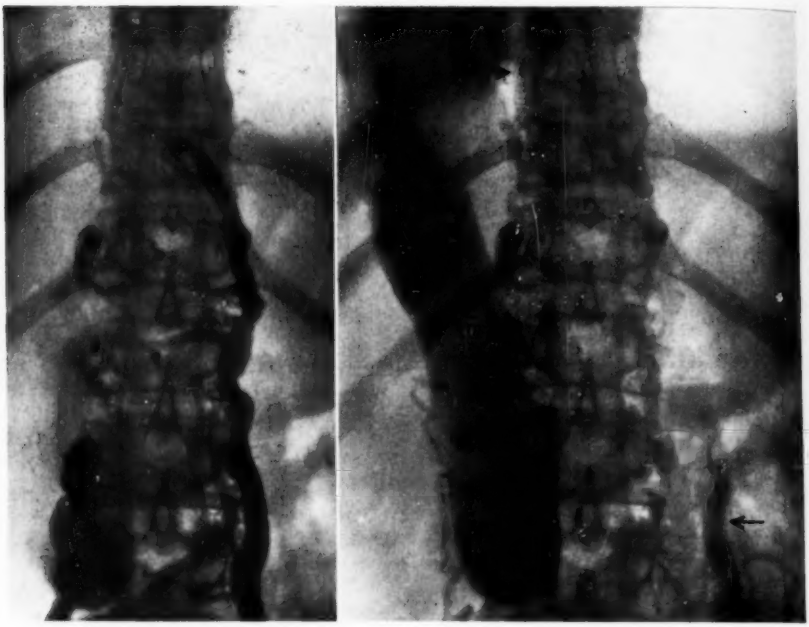
a b

Fig. 4. Male, aged 23. Six weeks after ligation of inferior vena cava. a) 3 sec after beginning of injection. Part of inferior vena cava above ligation fills with contrast medium by way of the collateral circulation through both lumbar ascending veins, the iliac branch of the right iliolumbar vein, lumbar veins, and the external and internal venous plexuses. Part of inferior vena cava below ligation and cranial parts of both common iliac veins do not fill, probably because of postoperative thrombosis. The left spermatic vein is filled. b) 11 sec later. Diluted contrast medium appears in the 8 mm wide, paravertebrally situated inferior mesenteric vein (←), which crosses the spine at level of L2 and enters the portal vein. Relatively thin layer of diluted contrast medium in portal vein (↑), practically none in inferior vena cava.

In two other cases (Figs. 4b and 6b) it was possible to observe the emptying of a part of the contrast medium from the inferior vena cava system into the portal system through the haemorrhoidal plexuses. We could not find any description of the roentgenologic demonstration of this collateral route in living human subjects in the available literature, though it is well known anatomically.

In our material the lumbar veins system (ilio-lumbar veins, lumbar ascending veins, lumbar veins) and that of the external and internal venous vertebral plexuses were the most important for the development of the collateral circulation (Figs. 2a, 3a, 4a, 5 and 6). They were demonstrated in all five cases, although the vertebral plexuses filled in one case (Fig. 6) to a lesser extent.

The spermatic, and utero-ovarian veins were filled with the contrast medium in 4 cases, once on both sides (Fig. 2b), and three times only on the left side (Figs. 4b, 5b and 6b). In 3 cases their calibre was small, and only in 1 did it reach the thickness of a pencil (Fig. 5b).



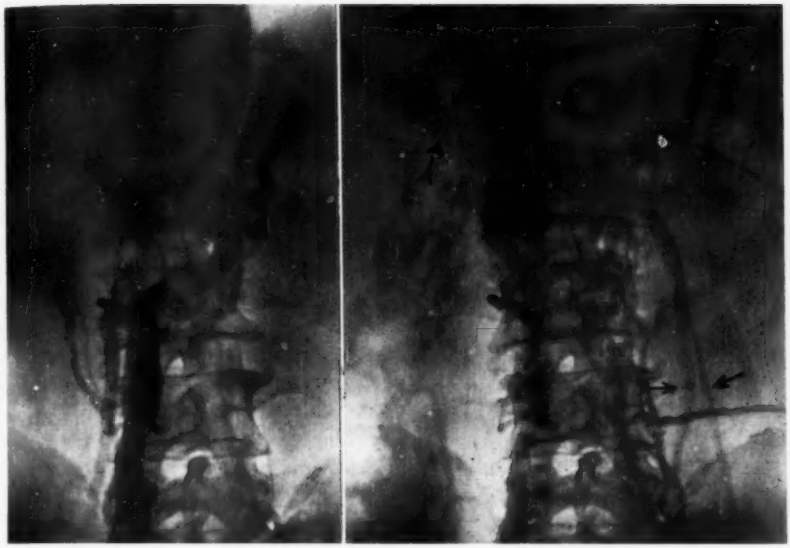
a b

Fig. 5. Male, aged 39. Fifteen weeks after ligation of inferior vena cava. a) 3 sec after beginning of injection. Contrast medium appears in inferior vena cava above point of ligation, passing through system of lumbar veins, especially the wide lumbar ascending veins. The external and internal vertebral venous plexuses also take part in the collateral circulation. b) 9 sec later. Inferior vena cava is enormously widened, its diameter reaching 4 cm. Small amount of contrast medium enters azygos vein (→). Left spermatic vein widened and tortuous (←).

The collateral circulation through the azygos and hemiazygos veins was demonstrated in 1 case (Fig. 3a), while in another it occurred only through the azygos vein (Fig. 5b). Even in these cases we gained the impression that only a small quantity of the contrast medium empties in this way into the superior vena cava.

The veins of the anterior and lateral abdominal and thoracic walls were of almost no importance for the collateral circulation.

The part of the inferior vena cava below the ligation did not fill with contrast medium in 3 cases probably because of postoperative thrombosis. In the first of these cases (Fig. 3a), the occlusion reached from the point of the ligation of the inferior vena cava to the junction of the common iliac veins. In the second case (Fig. 4a) the filling defect continued into both



a b

Fig. 6. Male, aged 49. Twelve weeks after ligation of inferior vena cava. a) 4 sec after beginning of injection. Contrast medium injected into both internal saphenous veins and passes through right common vein into part of inferior vena cava below ligation; this shows some irregularities in shape and width. Left common iliac vein does not fill. Lumbar veins system is better seen on right side. b) 11 sec later. Inferior vena cava above ligation still filled with contrast medium (⤇). Lumbar veins system now better seen on left side. External and internal vertebral venous plexuses take a lesser part in the collateral circulation. Left spermatic vein shown (←), inferior mesenteric vein (⤜), and portal vein (⤜ ⪡) filled with diluted contrast medium.

common iliac veins. In the third case (Fig. 5), it was not possible to ascertain the extent of the occlusion because only a small part of the region below the ligation was shown in the films. In 1 case (Fig. 6a) the part of the inferior vena cava below the ligation showed some irregularity in shape and width (perhaps due to recanalisation), since the whole left common iliac vein was obliterated. Only in 1 case (Fig. 2a), were there no pathologic changes in the part of the inferior vena cava below the ligation and in both common iliac veins. None of these four patients showed signs of thrombosis prior to the ligation.

It may well be said that in all our cases nearly all the contrast medium — injected into the internal saphenous veins — was emptied through the collaterals into the inferior vena cava above the point of the ligation. It is surprising how quickly the contrast medium reached the upper two-thirds

of the inferior vena cava despite the ligation; it took 2 to 3 sec in three cases and 4 to 6 in another two.

Stasis of the contrast medium in the part of the vena cava inferior above the point of the ligation was well marked in 2 cases, so that its shadow was dense even 20 to 21 sec after the beginning of the injection; in another 2 cases the contrast medium was hardly visible 14 to 15 sec after the beginning of the injection. In 1 case in which the serial films were completed 15 sec after the beginning of the injection, sufficient contrast medium was seen in the part above the ligation in the last film. Reflux in the hepatic veins was present in all 5 cases. It was marked in 3 cases (Figs. 2b, 3b and 6b).

In those cases in which the inferior vena cava filled quickly and emptied relatively rapidly, the clinical effect of the ligation was poor. The result of the operation was better in the three cases in which the emptying of the inferior vena cava was slowed down.

Discussion

The type of collateral circulation after ligation of the inferior vena cava found by the present authors in cardiac decompensated patients differs somewhat both from the type reported by SURINGTON and JONAS and from that described by HELANDER and LINDBOM. The cause of these differences would seem to lie in the kind of patients and the technique employed. SURINGTON and JONAS (whose publication on a roentgenologic study of the collateral circulation after ligation of the inferior vena cava seems to be the only paper on this subject) investigated patients with venous thrombosis in the lower extremities and pelvis, in which the ligation was performed to prevent a recurrence of pulmonary emboli. In these patients the ligation was carried out as an emergency procedure, *i. e.* in a venous system having no special disposition for the development of a collateral circulation. Conversely, in patients with chronic cardiac decompensation, stasis in the inferior vena cava system and its collaterals existed prior to ligation. The dilation of the whole system, caused by the stasis favours a full development of the collateral circulation after the ligation. This may be the reason why it was possible in our material to demonstrate the collateral circulation through the reno-azygo-lumbar canal and through the portal system. HELANDER and LINDBOM, using a football bladder to produce temporary occlusion of the inferior vena cava, probably compressed the reno-azygo-lumbar canal and the superior haemorrhoidal vein and made contrast filling of the above-mentioned collaterals impossible.

Post-operative thrombosis of the inferior vena cava below the point of ligation seems to be a common complication after the operation. The oc-

clusion may spread from the inferior vena cava into both common iliac veins.

The coincidence of slow emptying of the inferior vena cava and good clinical effect after the ligation deserves further investigation. In the cases with relatively rapid emptying of the inferior vena cava and poor clinical effect, we gained the impression that owing to the extensive collateral circulation the circulatory conditions in the upper two-thirds of the inferior vena cava were not essentially changed after the ligation. This may explain the absence of clinical improvement and at the same time the question arises whether it is of any use performing the operation under such anatomic conditions. Although we are concerned with facts, we cannot but present them for the time being with reserve. Only further investigations, carried out in a larger number of patients, are likely to prove whether there exists a causative relation between the clinical effects of the ligation on the one hand, and the type and speed of the collateral circulation on the other.

If such a relation could be shown, temporary occlusion of the inferior vena cava by the introduction of a rubber balloon into the vein itself, as described by NORDENSTRÖM, might be used for the purposes of prognosis. Prior to forming ligation of the inferior vena cava, the latter should be visualized both without and with temporary occlusion. We should thus be able to establish preoperatively both the type and speed of the collateral circulation likely to develop after the ligation. It is probable that quite a number of unnecessary operations would be avoided.

SUMMARY

Ligation of the inferior vena cava after CossIo and PERIANES was performed in 30 decompensated cardiac patients, and in 5 of these postoperative venography of the inferior vena cava was carried out. The type of collateral circulation which develops after the liga tion is described and discussed with due regard to anatomic conditions. The possibility and value of the preoperative determination of the type and speed of the collateral circulation likely to develop after the ligation are pointed out.

ZUSAMMENFASSUNG

Unterbindung der Vena cava inferior ad modum CossIo und PERIANES wurde bei 30 dekompensierten herzkranken Patienten durchgeführt; in 5 dieser Fälle wurde eine postoperative Venographie der Vena cava inferior ausgeführt. Der Typus des Kollateralkreislaufes, welcher sich nach der Unterbindung ausbildet, wird beschrieben und unter Berücksichtigung der anatomischen Gesichtspunkte diskutiert. Die Möglichkeit und der Wert der präoperativen Bestimmung des nach der Unterbindung wahrscheinlich auftretenden Typus des Kollateralkreislaufes sowie dessen Geschwindigkeit werden hervorgehoben.

RÉSUMÉ

Trente malades en décompensation cardiaque ont subi une ligature de la veine cave inférieure suivant le procédé de Cossio et Perianes; une phlébographie post-opératoire de la veine cave inférieure a été pratiquée sur cinq d'entre eux. Les auteurs décrivent le type de circulation collatérale qui se développe après la ligature et l'étudient au point de vue anatomique. Ils soulignent la possibilité et l'intérêt de préciser avant l'operation le type et la rapidité de la circulation collatérale qui se développera vraisemblablement après la ligature.

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A SIMPLE METHOD OF CATHETERIZATION OF THE SPLEEN AND LIVER

by

Sven Ivar Seldinger

A simple device consisting of polyethylene tubing over a puncture needle (Fig. 1) has been developed for the injection of contrast medium in lieno-portal venography. It is now regularly employed and no complications have arisen.

The instrument is made up in the manner illustrated in Fig. 2. An ordinary puncture needle and polyethylene tubing of slightly larger bore form its essential parts. The tubing is slipped over the whole length of the needle, or preferably over a metal wire of the same diameter and with a blunt end. The free end of the tubing is stretched so that the diameter and wall thickness become considerably reduced. The tubing is withdrawn and cut off at the point where the wall is thinnest and exactly fits the needle; the outer diameter of the catheter at this point will be very little larger than the diameter of the needle (Fig. 1, below). The other end is cut off so that the length of the catheter corresponds to the length of the needle, measured from the butt to about one mm from the tip, and is thereafter shaped by heating to fit the conventional polyethylene catheter adapter (Fig. 1, middle). The catheter is then threaded upon the needle, the adapter fitted, and the instrument is complete.

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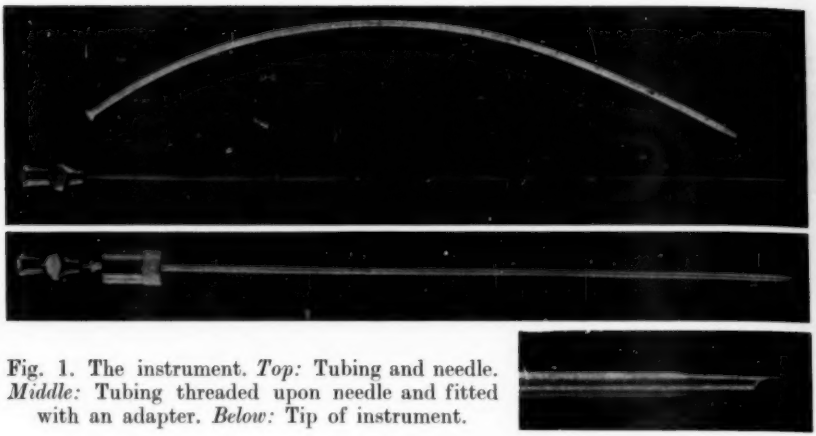

Fig. 1. The instrument. *Top:* Tubing and needle. *Middle:* Tubing threaded upon needle and fitted with an adapter. *Below:* Tip of instrument.

There is some resistance to the instrument only as it transverses the skin, wherefore a small incision should be made at the puncture site. Splenic puncture (Fig. 3) is performed during apnoea and the needle withdrawn from the catheter before the patient is allowed to breathe again. A stopcock is screwed on to the adapter and the catheter is filled with saline solution.

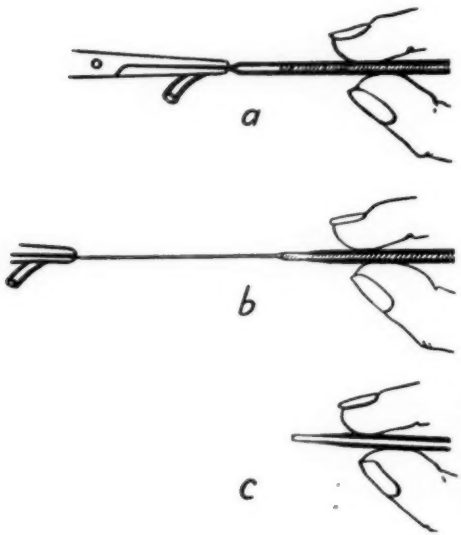

Fig. 2. Method of moulding tip of catheter. a) Needle, or a metal wire of the same diameter, is inserted into tubing until its tip lies a short distance from one end of latter. b) Remainder of catheter is stretched so as to reduce diameter and wall thickness. c) Catheter is cut off where it fits needle exactly.

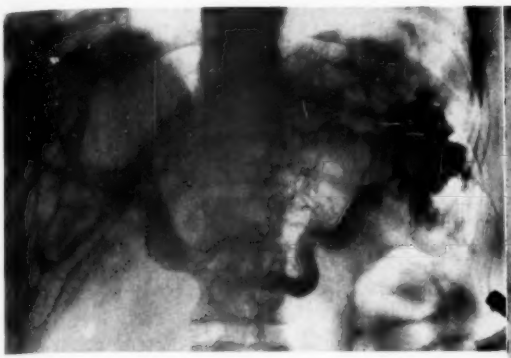

Fig. 3. Lieno-portal venography. Catheter in spleen. A pancreatic cyst obstructs splenic vein; the gastric veins provide the collateral circulation.

Fig. 4. Percutaneous transhepatic cholangiography. The tip of catheter is in a widened intrahepatic duct. The bile duct is occluded by a pancreatic tumour.

This technique is used in order to avoid damage to the spleen by the needle during respiration or movements of the patient. Many radiologists consider that risk so important that they perform the whole procedure — puncture, injection of the contrast medium, and withdrawal of the needle — during the same period of apnoea. By employing the catheter, the entire investigation, including measurement of the pressure in the spleen, can be performed without undue haste. The puncture of a small spleen is facilitated if the patient is placed in oblique position so that the central ray during fluoroscopy is directed tangential to the area where the spleen is in contact with the abdominal wall. The puncture completed, the patient may be moved into any position desired without risk of damage by the puncture instrument.

The instrument has also been used in a series of percutaneous transhepatic cholangiographies carried out according to the technique described by CARTER and SAYPOL (1952) (Fig. 4). It is still too early to judge whether complications in such liver punctures are avoided by using the 'needle catheter' in place of a needle.

SUMMARY

A 'needle catheter' for the injection of contrast medium into parenchymatous organs (spleen, liver) is described. It has proved suitable for lieno-portal venography and transhepatic cholangiography.

ZUSAMMENFASSUNG

Ein "Nadelkatheter" zur Injektion von Kontrastmittel in parenchymatöse Organe (Milz, Leber) wird beschrieben. Er hat sich für die lieno-portale Venographie und für die transhepatische Cholangiographie als geeignet erwiesen.

RÉSUMÉ

L'auteur décrit une »aiguille cathéter» pour l'injection de moyen de contraste dans des organes parenchymateux (rate, foie). Cette aiguille convient pour la spléno-portographie et pour la cholangiographie transhépatique.

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IMPAIRMENT IN INCISOR TEETH FORMATION FOLLOWING ADMINISTRATION OF HIGH ACTIVITY P^{32} IN WEANLING RATS

by

Göran C. H. Bauer, Arvid Carlsson and *Bertil Lindquist*

The radiation effect on various metabolic processes of radioactive isotopes merits study for several reasons. Human or animal contamination with radioactive elements may occur following not only an explosion of an atomic bomb but also from laboratory accidents. Radioactive isotopes are extensively used for metabolic investigations and are administered for therapeutic or diagnostic reasons. If the radiation impairs or alters the normal metabolic pattern, erroneous conclusions may be derived from isotope experiments.

The present experiment was planned to study the radiation effects of high activity P^{32} on bone growth and incisor teeth formation following the administration of the isotope to rats. A severe impairment of the formation of incisor teeth was found following the administration of a dose of P^{32} which had but a slight effect on the growth of the long bones.

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Table

Ash weights and activity values of the tibiae and the incisor teeth following the subcutaneous injection of 10 or 100 μC P^{32} in weanling rats.

Interval after injection	2-Day		10-Day		30-Day	
	Low dosage animals	High dosage animals	Low dosage animals	High dosage animals	Low dosage animals	High dosage animals
Number of animals	5	3	5	4	5	3
Weight of animals (grams)	18.0 (1.5)	16.7 (1.2)	28.6 (1.6)	27.5 (1.8)	71.0 (5.5)	59.7 (6.0)
Tibia length (mm)	14.4(0.36)	14.5(0.12)	19.5(0.30)	18.6(0.32)	26.3(0.60)	25.1(0.90)
Lower incisor length (mm)					18.1(0.42)	14.4(0.94)
Tibia ash weight (mg) ...	7.8 (0.82)	8.0(0.93)	24.6 (2.1)	26.4 (3.7)	84.3 (7.1)	77.4 (6.8)
Incisor ash weight (mg) ..	9.3 (0.35)[1]	8.2(0.75)[2]	28.1(0.35)	24.6 (1.0)	67.2 (4.2)	45.5 (3.2)
Tibia activity (percentage of dose) .	1.10(0.08)	1.09(0.09)	1.82(0.08)	1.61(0.09)	3.95(0.11)	2.95(0.25)
Incisor teeth activity (percentage of dose) .	1.06(0.11)[1]	0.809(0.074)[2]	2.91(0.10)	2.08(0.12)	3.51(0.18)	3.55(0.77)

In each animal the right and left tibiae formed one sample and the four incisor teeth formed one sample. Accuracy: Of activity measurements better than ±3 per cent at each observation, of ash weights ± 0.1 mg, of body weights ± 1 g, and of length measurements ± 0.1 mm.

[1] 2-day incisors from 3 animals. — [2] 2-day incisors from 2 animals.

Experiments

The experimental series consisted of twenty-five 10-day-old rats belonging to five different litters of an inbred strain. Each rat received 10 or 100 μC carrier-free P^{32} in sterile physiologic NaCl solution subcutaneously. Fifteen rats were given the 10 μC dose and ten rats the 100 μC dose. (The activity specification from the Radiochemical Centre, Amersham, England was checked by K. LIDÉN.) After injection, the rats were kept with their mothers in ordinary cages, each litter separated in its own cage. The rats received a standard diet containing all known food constituents in adequate supply. The rats were killed with an overdosage of ether 2, 10, and 30 days following administration of the isotope.

Immediately after death of the animals, the right and left tibias (one sample), and the incisor teeth (one sample) were dissected free from adhering soft tissues. Each sample was ashed for 2 hours in an electrically heated muffle, the ash was weighed, and then dissolved in nitric acid. The volumes of the nitric acid solutions were chosen to permit aliquots to be counted with an end-window G. M. tube connected to a rate meter. The procedure followed was that described by BAUER 1954. (See also CARLSSON 1951 for details of the adopted counting technique.)

By reference to a standard, the activity measurements were expressed as a percentage of the dose recovered from the various samples.

Results

Body weight. It is seen from the Table that the body weight of the high dosage animals was slightly less than of the low dosage animals. This difference was statistically significant at the 30-day interval ($P<0.005$).

Bones. The high P^{32} dosage had no definite effect on the increase in the ash weight and the length of the tibia. The tibia activity was about the same in the high as in the low dosage animals at the 2- and 10-day intervals. At the 30-day interval the tibia activity was 29 per cent lower in the high than in the low dosage animals ($P<0.001$).

Incisor teeth. It is also seen from the Table that the high P^{32} dosage had impaired the growth of the incisor teeth. The 10-day incisor teeth ash weight was thus 12.5 % lower in the high than in the low dosage animals ($P<0.01$), and this difference was even more marked at the 30-day interval. The impairment in the growth of the incisor teeth is evident also by a comparison of the length of the 30-day lower incisor teeth (14.4 and 18.1 mm in the high and low dosage rats, respectively).

The activity of the 2- and 10-day incisor teeth was 24 and 28 per cent lower in the high than in the low dosage rats, respectively, while at the 30-day interval the incisor activity was about the same in the two groups investigated. The last-mentioned observation is probably explained by the assumption that the incisor activity of the low dosage rats had already been reached by the normal attrition process, while in the high dosage rats the impairment in tooth formation had resulted in poorly developed incisors which it does not seem likely that the animals had used for gnawing.

In support of this assumption it was found that the cross-sectional size of the incisor tips was markedly less in the high dosage animals, indicating that the tips had been formed at a lower age (*cf.* SCHOUR and MASSLER 1942). This explanation makes even more impressive the difference in the ash weight and incisor length observed at day 30.

Discussion

The relatively marked impairment of the incisors may possibly be explained by comparing the geometrical arrangement of the growth areas of the incisor teeth with that of the bones. In the incisor new tissue is formed on the inner periphery of a cylinder (or rather a cone), and the tissue-forming cells are thus reached by the radiation from the whole circumference of the surrounding newly-formed calcium-phosphorus salt. The radiation effect on the cells will therefore be more marked in the incisors than in the bones where the radiation from the newly-formed bone-salt does not reach the tissue-forming cells to the same extent.

SUMMARY

A severe impairment in the formation of the incisor teeth followed the subcutaneous injection of 100 μC P^{32} in weanling rats. This dose had but a small effect on the normal growth of the long bones. The difference in radiation effect is tentatively attributed to the geometric arrangement of the areas of growth in the incisors and bones.

ZUSAMMENFASSUNG

Subkutane Injektion von 100 μC P^{32} erzeugte bei entwöhnten Ratten eine ernsthafte Verschlechterung der Ausbildung der Schneidezähne. Die benutzte Dosis hatte auf das normale Wachstum der langen Röhrenknochen nur geringe Wirkung. Der unterschiedliche Strahleneffekt wird präliminär der geometrischen Anordnung der Wachstumzonen in den Schneidezähnen und in den Knochen zugeschrieben.

RÉSUMÉ

L'injection sous-cutanée de 100 μC de P^{32} à des rats sevrés a entraîné de graves troubles de la formation des incisives. Cette dose n'a eu que peu d'effet sur la croissance normale des os longs. Cette différence d'effet des radiations est attribuée, à titre d'hypothèse, à la disposition géométrique des régions de croissance dans les incisives et dans les os.

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AUTORADIOGRAPHY AND RADIOACTIVITY MEASUREMENTS WITH HUMAN NEOPLASMS CONTAINING RADIOPHOSPHORUS

by

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Radiophosphorus, administered as inorganic phosphate, is taken up preferentially by some types of malignant cells, but the degree of concentration is not high relative to other radiosensitive tissues in the body. Activities which can be administered safely are therefore low (5 to 10 mC) and the corresponding specific activities of tumour tissue rarely rise above a few tenths of a microcurie per gram. The total mean radiation dose to a tissue containing initially 1 μC/g of P^{32} is approximately 600 rad (MITCHELL 1951), and no striking therapeutic effects on tumours of ordinary radiosensitivity can be expected following systemic administration of this isotope. Such limited degrees of concentration have some value for diagnosis and assessment of progress (LOW-BEER 1952), and possibly for the treatment of very radiosensitive lesions (RENFER 1955). The exact distribution of the radioactivity within a tumour is therefore of interest, but the levels of radioactivity attainable are not often sufficient for an autoradiograph of high resolution, particularly in view of the high energy of β-rays from P^{32} and their long range in

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photographic emulsion. Previously published autoradiographic work using P^{32} in human tissue includes that by STEINBERG and SELVERSTONE (1950) on brain tumours, by FRIEDELL and STORAASLI (1950) on metastatic carcinoma in bone, and by THOMAS, KROHMER and STORAASLI (1952) on tumours of the eye. An account of surface measurements made on human subjects was first published by MARINELLI and GOLDSCHMIDT (1942).

As well as its use in the treatment of polycythaemia rubra vera, P^{32} has occasionally been used at this clinic over the past six years in treatment of advanced or generalized malignant disease. In a few such cases, which form the material of this paper, we have made measurements of tissue radioactivity, and where possible have made autoradiographs. No attempt is made here to assess the therapeutic value of radiophosphorus.

Methods. P^{32} was administered by mouth in solution as orthophosphate. Measurements were carried out 24 hours later. In the earlier cases (Nos. 2 to 5) counting rates were measured by means of an end-window counter placed first over the cutaneous lesion and then over nearby normal skin. For lesions 3 mm thick or more, the ratio of counting rates is approximately equal to the ratio of radioactivity in the lesion to that in normal skin and subcutaneous tissue. Methods were then developed for making an absolute estimate of the radioactivity in the neoplasms, and in Case 6 this was done by comparison with a phantom containing an aliquot of the solution administered to the patient. In Cases 7 to 9, in which biopsy specimens were available, thin slices of the fresh tissues were cut, and compared under an end-window counter with a simulated P^{32} standard (Tracerlab-Boston, Mass., U.S.A.). Correction for thickness of sample was made by extrapolating to zero thickness according to an exponential relationship (GRAY 1949) which was found to fit our observations. In the last two cases (10, 11), weighed pieces of the tissue were dissolved, made up to a standard volume, and compared with a diluted aliquot of the original radioactive solution given to the patient. The method of dilution was shown to be free from error due to adsorption on to the walls of the vessels. A satisfactory reagent for solution of the tissues was hot concentrated sulphuric acid, to which was added at intervals a few drops of concentrated nitric acid. Adjacent pieces of tissue were used for histology and autoradiography.

Autoradiographs at low resolution were made on Ilfex roentgen film, either with the fresh specimen, the film remaining in its opaque envelope and with the additional protection of an aluminium foil (7 mg/sq.cm), or with paraffin-embedded blocks and sections in contact with the emulsion. Freeze-drying apparatus was only available for the specimen from

the last case of the series; the earlier specimens therefore lost most of the soluble phosphorus before embedding. For microscopic study, some autoradiographs were made by the stripping film technique of DONIACH and PELC (1950). The 'coated autograph' technique was also used, melted emulsion being painted on to slides carrying the sections, in a layer thick enough to show individual electron tracks.

Clinical notes

Case 1. Carcinomatosis of skin of chest. A man aged 70 presented with carcinoma of the skin of his chest, and axillary and supra-clavicular glands. He had received a gunshot wound at the site of the growth 37 years before, which was followed by chronic infection, but had been well healed for 29 years.

He was treated with palliative roentgen doses to the primary and to the glands, and was also given P^{32}, 5 mC. The response to roentgen rays in the treated areas was satisfactory. Further widespread skin lesions developed during the following few months, and he died from pulmonary metastases 6 months after the first treatment.

Case 2. Carcinoma of ovary. A married woman aged 57 had laparotomy and removal of a large ovarian growth. Blood-stained ascites was present and multiple nodules of growth were found on the pelvic peritoneum. The histology was a tubular and papillary columnar-celled carcinoma. Roentgen therapy was given to a central pelvic dose of 2,600r in overall time 23 days by anterior and posterior fields 20×15 cm. She remained well until 8 months later a tumour developed at the umbilicus and ulcerated. Ascites reappeared at the same time. P^{32}, 8 mC, was given, and, after biopsy at 24 hours, a single roentgen treatment (1,500r) was given to the umbilical growth, which retrogressed almost completely. There was nausea and some vomiting for 5 weeks after the radiophosphorus. The patient died 12 months after the first roentgen treatment.

Case 3. Carcinoma of breast. An unmarried woman aged 54 presented with very advanced ulcerating carcinomatosis of both breasts, chest wall, axillary and supra-clavicular glands, and a pleural effusion. The liver was not enlarged. The last menstrual period was 4 years before. She was given palliative deep roentgen therapy with injections of tetrasodium 2-methyl-1 : 4-naphthohydroquinone diphosphate (Synkavit) as a radiosensitizer, and testosterone propionate 100 mg daily. There was little local response to a radiation dose of 1,700r (applied) in 28 days, and her general condition deteriorated. After an interval of one month during which there was no improvement, an attempt at therapy with P^{32} was started. Injections of testosterone propionate and Synkavit were continued daily. Three doses of P^{32}, 10 mC, 8 mC, 8 mC, were administered at intervals of 2 weeks. There was a slight temporary improvement, but the patient died 4 months after the first roentgen treatment.

Case 4. Malignant haemangioma. A married woman aged 52 had a lump removed from the right scapular region which had been present for one year. A month later she developed multiple subcutaneous recurrences in and around the scar, and widespread pulmonary metastases. A test dose of P^{32} showed only moderate selective uptake by the tumours (Table I) and treatment was given by conventional roentgen radiation. Some retrogression of the tumours was obtained and her general condition improved temporarily. She died 5 months after the first roentgen treatment with multiple metastases in lungs, liver, and bones.

Table I

Relative measurements, in vivo, of radioactivity in neoplasms.

Case	Activity administered (mC)		Ratio of counting rates lesion/skin
	Total dose	Per kg body weight	
1. M. Squamous cell carcinoma of skin....	5.0	0.07	> 1[1]
2. F. Carcinoma of ovary, skin metastasis	7.8	0.15	2
3. F. Carcinoma of breast	8.0	0.14	
Skin lesions, ulcerated			> 2
Skin lesions, erysipeloid			> 2
4. F. Malignant haemangioma	1.0	0.014	
Large lesion			2
Small lesions			3
5. F. Reticulosarcoma: skin lesions	10.0	0.15	
Right leg			1.5
Right breast			1.5
Left cervical			1.1

[1] Autoradiographic evidence.

Case 5. Reticulosarcoma. A married woman aged 42 presented with generalised gross enlargement of superficial lymph nodes, some of them ulcerated. Liver and spleen were not enlarged. There was collapse of the right lung and a pleural effusion. She had had generalised eczema since puberty. There was a strong family history of skin disease. Biopsy of an involved area of skin showed infiltration with malignant cells regarded as either reticulosarcoma or mycosis fungoides. Treatment by roentgen rays and by radiophosphorus was started immediately, but the patient died in 3 weeks from bronchopneumonia. One of the gland areas had shown some retrogression after 500r of roentgen radiation. Autopsy showed widespread deposits of reticulosarcoma in lymph nodes, mammary glands, muscles, and viscera.

Case 6. Malignant melanoma and terminal leukaemia. A man aged 55 presented with a melanoma on the sole of the foot and a malignant gland in the groin. At operation, the tumour was removed with a wide margin, and block dissection of the inguinal and popliteal glands was performed. 6 months later the external iliac glands were involved, followed by local recurrence on the sole of the foot. Three doses of P^{32}, 10 mC, 6 mC, 5 mC, were given at weekly intervals, with daily injections of Synkavit as radiosensitizer. The estimated total radiation dose to the malignant tissue was 700 rad. This was followed by conventional radiotherapy, 3,000r skin dose in 8 days to the lesion on the foot and to the inguinal and external iliac glands. There was partial retrogression of the lesions in both sites and the patient returned to work for 5 months, then was ill with pneumonia for 3 months, and returned to work for a further 18 months. He gradually put on 42 lb (19 kg) in weight. During this time stationary or very slowly progressive lesions were present on the foot, which did not respond to radiotherapy. Three years and 3 months after the first treatment he developed acute myeloid leukaemia and died in one month. Autopsy showed the presence of malignant melanoma in the lesions on the foot and in a small nodule in the lung. There was widespread leukaemic infiltration in lymph nodes and other organs.

Table II

Absolute measurements of radioactivity in neoplasms.

Case	Activity administered (mC)		Mean activity of specimen (μC/g)	Mean D.A.R.
	Total dose	Per kg body weight[1]		
6. M. Malignant melanoma, skin nodules	10.0	0.12	—	4.5
7. M. Lymphosarcoma, involved axillary gland	2.8	0.060	0.054	0.95
8. F. Malignant haemangioendothelioma. Lymph node (non-malignant)	10.0	0.16	0.16	1.0
9. M. Reticulosarcoma. Involved lymph node	5.0	0.073	0.29	4.0
10. M. Malignant melanoma, lymph node metastases	9.4	0.11	0.62 0.22 0.09	5.6 2.0 0.8
11. F. Reticulosis	1.0	0.019		
Involved lymph node			0.064	3.4
Sternal marrow			0.013	0.7
Blood			0.013	0.7
Fat			0.008	0.4

[1] Corrected for radioactive decay up to the time of biopsy.

Case 7. Lymphosarcoma. A man aged 70 presented with loss of weight, multiple enlarged lymph nodes, and enlargement of liver and spleen. Mediastinal glands were involved and caused respiratory symptoms. A test dose of P^{32} followed by biopsy showed no useful concentration in an involved gland. Palliative radiotherapy was given to the largest gland masses, which responded to doses of 1,000r, and to the mediastinum. There was a marked improvement in his general condition, which lasted 2 years and his weight increased by 14 lb (6 kg). He died from mediastinal growth 3 years and 3 months after the first treatment.

Case 8. Malignant haemangioendothelioma. A married woman aged 35 complained of pain in her arm of 20 months duration. The head of the humerus was destroyed by growth and multiple haemangioendotheliomata were present in the skin; there was enlargement of cervical lymph nodes, and of the liver, and bilateral papilloedema and retinal haemorrhages. There was evidence of possible involvement of cerebellum and of adrenal glands. Radiophosphorus, 10 mC, was administered; there was, however, no evidence of useful uptake in the skin lesion biopsied. Conventional radiotherapy was given to the head of the humerus (1,000r central in 8 days) and to the cerebellum (500r minimum in 8 days). This was followed by partial recalcification in the humerus and complete relief of pain. The patient lived for three years after the first treatment. For the greater part of the time there was a recurrent ascites which was treated at different times by paracentesis, external radiation to the abdomen, and intraperitoneal injection of radioactive colloidal gold. She died from generalised anasarca.

Case 9. Reticulosarcoma. This case was shown to the Section of Dermatology of the Royal Society of Medicine by WHITTLE, LYELL and CHURCH in 1950. The patient was a

farmer aged 45 who developed in succession a number of enlarged lymph nodes and later skin lesions, subcutaneous tumours, oedema, pleural effusion, and enlargement of spleen and liver. The sternal marrow and peripheral blood always showed eosinophilia.

The skin lesions and superficial lymph nodes were very radiosensitive, and the disease was kept under control for two years by superficial roentgen doses of 250r or 500r. Deep roentgen therapy was given to spleen, liver and deep lymph nodes. Other treatments which gave temporary benefit were antihistamine drugs, ACTH, and cortisone. Finally, when his general condition was deteriorating fast, P^{32}, 5 mC, was given. The uptake in an involved lymph node was relatively high (Table II), and there was a definite improvement for a few days. The estimated radiation dose in the lesions due to the first administration of P^{32} was 160 rad. He died only a few days after a second dose of P^{32} (5 mC), 2 years and 3 months after the first roentgen treatment.

Case 10. Malignant melanoma. A man aged 74 presented with a mass in the axilla. He had had a wart removed from the wrist 18 months before, followed by excision of an epitrochlear gland. Deep roentgen therapy was given, minimum tumour dose 2,500r in 26 days followed by a further 1,000r a month later. This caused incomplete retrogression of the gland mass. Other glands developed outside the treated area and block dissection of the axilla was decided upon as a palliative measure. A therapeutic dose of radiophosphorus was given before operation with the object of assessing uptake into the malignant tissue. The uptake was relatively high. The patient remained well for 2 months, and then rapidly deteriorated and died from widespread recurrence 8 months after the first roentgen treatment.

Case 11. Reticulosis. This case was shown to the Royal Society of Medicine by Whittle and Lyell (1951). At that time the patient had multiple cutaneous nodules with lymphocytic infiltration of the corium, tentatively diagnosed as 'symmetrical lymphocytoma'. She also suffered from diabetes mellitus, which was easily controlled by diet and small doses of insulin. Later lymphadenopathy developed and gradually became generalised, with splenomegaly and hepatomegaly. At this stage a test dose of radiophosphorus was given followed by biopsy of an axillary lymph node. The uptake of P^{32} was not considered high enough to give prospect of useful treatment by this means. Roentgen therapy was given to a number of lesions with good effect. She died of bronchopneumonia 8 months after the first roentgen treatment. The classification of this reticulosis remained in doubt during life; the post mortem histological diagnosis was polymorphic reticulosarcoma.

Results. Particulars of the activities administered, and the measured activities of the neoplasms, are given in Tables I and II. In each of the 5 cases in Table I, for which only relative measurements were made, the radioactivity in the malignant lesion was higher than that in the area of normal skin with which it was compared. In the 6 cases in Table II, direct measurement of the radioactivity of the specimen allowed calculation of the 'Differential absorption ratio' (D.A.R.) as defined by Marinelli, Quimby and Hine (1948). This is the ratio of the specific activity of the tissue in question, to the specific activity it would have at the same time if all the administered radioactivity were uniformly distributed throughout the body, and if none had been excreted. The D.A.R. therefore gives a rather conservative estimate of the relative avidity of the tissue for radiophosphorus. In 4 of the 6 cases, the malignant tissue had a D.A.R. very significantly greater than one. The highest value was 5.6.

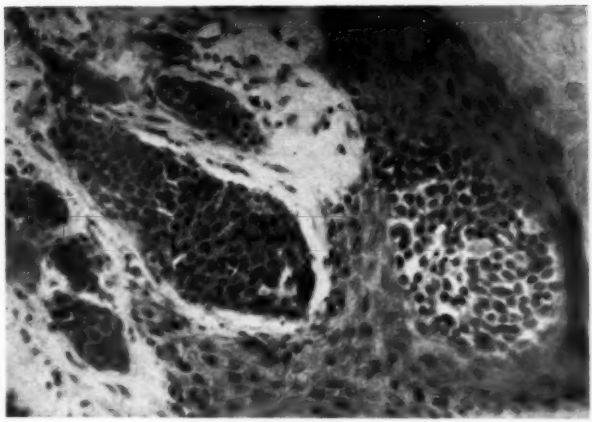


Fig. 1. Case 1. Squamous cell carcinoma of skin, section stained Feulgen. × 175.

Autoradiography

Case 1. Squamous cell carcinoma. Biopsies were taken at 24 hours and at 48 hours after administration of P^{32}, 5 mC. The histology was a poorly differentiated squamous carcinoma (Fig. 1). Electron tracks in the 'coated autographs' showed radioactivity in the epidermis of normal skin, but not in the dermis. The radioactivity was higher in carcinoma than in normal epidermis, and was highest in some superficial groups of cells with abundant mitoses. It was also high in tissue showing an inflammatory response to invading carcinoma. The dermis underlying carcinoma was slightly radioactive; keratin and extravasated blood showed little or no radioactivity. These features were seen in both the 24-hour and the 48-hour specimens, and no difference was demonstrated between the two.

Case 2. Carcinoma of the ovary. In vivo measurements at 24 hours showed that an ulcerated nodule at the umbilicus had twice the radioactivity of normal skin. A biopsy was taken, but the radioactivity was not great enough to give an autoradiograph; probably a large proportion of the radiophosphorus was removed during fixation and dehydration. The specimen included actively growing carcinoma with abundant mitoses.

Case 8. Malignant haemangioendothelioma. Radiophosphorus was administered, and 24 hours later a lymph node and a cutaneous nodule were removed from the neck. Half of the lymph node was used for activity measurements, and the remainder of the specimens for histology and autoradiography. Unfortunately from the point of view of the measurements, the lymph node did not contain malignant tissue. Parts of the lymph node showed a minimal autoradiograph by the stripping film technique, amounting to 8 ± 4 grains (above background) per 100 square microns. Calculation shows that this is consistent with the measured radioactivity of the specimen. The cutaneous nodule, which histologically was haemangioendothelioma, also gave a minimal autoradiograph. This nodule was too small for a direct measurement of radioactivity.

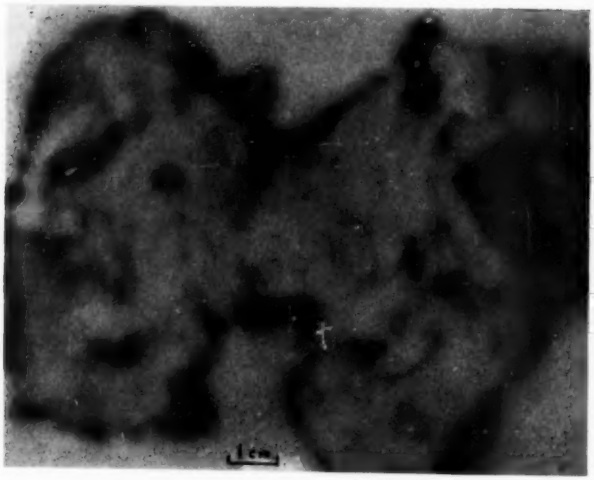
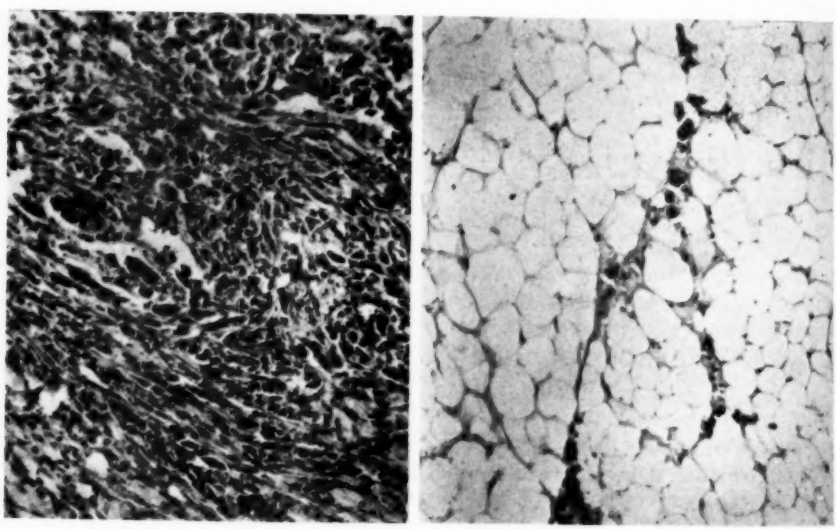


Fig. 2. Case 10. Malignant melanoma — metastases infiltrating fat. Autoradiograph of fresh specimen on roentgen film.



a b

Fig. 3. Case 10. Malignant melanoma. Sections stained haematoxylin and eosin. × 110. a) Solid tumour. Region of high radioactivity. b) Fat infiltrated with melanoma. Region of intermediate radioactivity.

Case 9. Reticulosarcoma. Biopsy of an involved lymph node 24 hours after administration of P^{32}, 5 mC, showed a specific activity of 0.29 μC/g. Stripping film autoradiographs showed a just-detectable increase of the silver grains over the sections, which seemed, if anything, to be more marked over the stroma than over the close-packed malignant cells.

Case 10. Malignant melanoma. Radiophosphorus was administered 24 hours before the operation of block dissection of the axilla. The tissue which was removed consisted of a mass of black cystic nodules embedded in fat. Activity measurements were made on three different pieces of tissue and, in addition to stripping film autoradiography, a large slice of the specimen, unfixed, was laid on roentgen film (Ilfex) with an intervening protective layer of aluminium (7 mg/sq. cm). The autoradiograph so obtained is shown in Fig. 2. The regions of highest activity were those consisting of vascular melanomatous tissue. Necrotic regions and infiltrated fat showed intermediate activity, and normal fat showed no autoradiograph. These features were confirmed by stripping film autoradiographs, and by autoradiographs on roentgen film from the paraffin wax block. Photomicrographs of stained sections are reproduced in Fig. 3.

Case 11. Reticulosis. P^{32}, 1 mC, was given by mouth 24 hours before biopsy, and parts of the tissues removed were assayed for radioactivity, with the results shown in Table II. The activity in the lymph node was five times that in blood and sternal marrow. Autoradiography of the blocks after freeze-drying and embedding in paraffin wax showed that the retained activity was distributed through the pathologic tissue of the node (Fig. 4).

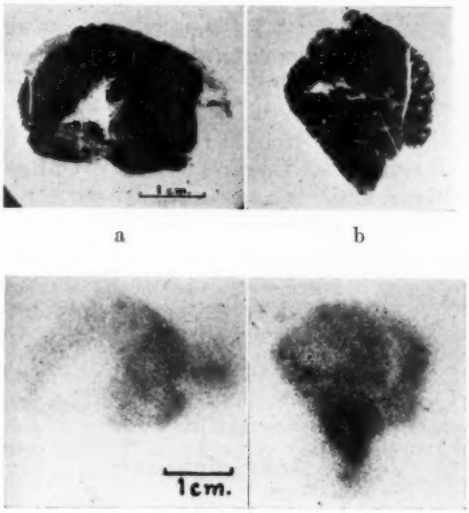


Fig. 4. Case 11. Reticulosis — lymph node. a—b) Photographs of stained sections c—d) Autoradiographs on roentgen film from corresponding paraffin blocks.

Discussion

The highest mean activity found in these specimens was 0.6 μC/g in Case 10, for 9 mC administered, and on a proportional basis would have been as high in Cases 9 and 11. This would deliver during decay and excretion with assumed total half-life of 11 days, a radiation dose of approximately 360 rad. Such a low dose can be of therapeutic value only in rare cases. For example the extremely radiosensitive lesions in Case 4 were kept in check for several years by tumour doses of the same order delivered by conventional roentgen methods. There are, however, other factors which, in a particular case, might operate favourably so that a larger dose could be delivered to tumour cells. The basis of systemic radio-isotope therapy is that the tumours take up more of the isotope than normal tissues, but within a tumour the distribution between stroma and malignant cells may be favourable. The distribution of radioactivity in Cases 1, 10 and 11 was favourable so that malignant cells had more, and stroma had less, than the average for the whole specimens. This factor would be of more value if the range of the emitted β-rays were short, so that a large proportion of the ionization due to a β-particle would be produced in the cell in which it originated. The β-rays of P^{32}, with 'half value layer' of about 1.8 mm in tissue of unit density (Rossi and Ellis 1952), do not approximate to this condition. Another phosphorus isotope, P^{33} (half-life 25 days), emits less energetic β-rays with 'half value layer' of the order of 120μ, and although this value is not small enough to be ideal, it seems probable that P^{33} would in these cases have been a more useful isotope for therapy than P^{32}. Unfortunately, P^{33} is not at present available in millicurie amounts. There is no other phosphorus isotope with a convenient half-life.

Another factor controlling relative radiation doses in different tissues is the time of retention of the isotope. Little is known of the variation of this in different tissues and in different cases, nor whether it can be varied artificially in any way. The early work of Kenney, Marinelli and Woodard (1941) showed that in some cases P^{32} is retained until physical decay is almost complete.

Acknowledgements

Our thanks are due to Professor J. S. Mitchell for his interest and advice, to our colleagues at the Radiotherapeutic Centre, Addenbrooke's Hospital, for their collaboration, and to Mr. J. L. Haybittle for collaboration in some of the measurements. One of us (A. F. P.) was supported financially for part of the time by a Beit Memorial Fellowship and for part by a Saltwell Scholarship of the Royal College of Physicians.

SUMMARY

Radioactivity measurements have been made in 11 cases of advanced malignant disease for which treatment by means of radiophosphorus, P^{32}, was attempted. In 5 cases counting was done *in vivo*, and in each case malignant cutaneous lesions contained more radioactivity than unaffected skin. In 6 cases biopsy material was available and estimates of the differential absorption ratio for the malignant tissue could be made. This ratio was approximately 1.0 in 2 cases, and was significantly higher in 4 cases. Stripping film autoradiographs were obtained in 5 cases in spite of low levels of radioactivity. The concentration of radioactivity was usually higher in malignant cells than in neighbouring non-malignant tissue, but in one case the opposite was true. The theoretical advantage of the other isotope of phosphorus, P^{33}, is mentioned, namely that its β-rays have a shorter range in tissue.

ZUSAMMENFASSUNG

In 11 Fällen von fortgeschrittenen bösartigen, mit P^{32} behandelten Geschwülsten wurden Messungen der vorhandenen Radioaktivität angestellt. In 5 Fällen, in denen die Messungen in vivo gemacht wurden, war die Radioaktivität in der Geschwulstzone höher als in der unbeschädigten Haut. In 6 Fällen konnte das Verhältnis der unterschiedlichen Absorption im Tumorgewebe an Probeexcisionen bestimmt werden. Das Verhältnis war in zwei Fällen ungefähr 1.0 in den anderen 4 Fällen war es signifikativ höher. Trotz der geringen Radioaktivität konnten in 5 Fällen Autoradiogramme hergestellt werden. Mit Ausnahme eines Falles war die Konzentration der Radioaktivität in den Krebszellen gewöhnlich höher als in normalem Gewebe. Zum Schluss wird der theoretische Vorteil eines anderen Radiophosphors, nämlich P^{33}, erwähnt. Dieser beruht auf der kürzeren Wirkungsdistanz seiner Betastrahlen im Gewebe.

RÉSUMÉ

Les auteurs ont fait des mesures de radioactivité dans 11 cas d'affection maligne où ils avaient essayé un traitement par le radiophosphore P^{32}. Dans 5 cas le comptage fut fait *in vivo*, et, dans tous ces cas, les lésions cutanées malignes étaient plus radioactives que la peau saine du voisinage. Dans 6 cas le rapport différentiel des tissus malins a pu être évalué sur des fragments biopsiques. Ce rapport était approximativement égal à 1 dans deux cas, et significativement plus élevé dans les quatre autres. L'autoradiographie a montré dans 5 cas, que la fixation radioactive était généralement plus élevée dans les cellules malignes que dans les tissus normaux. Les auteurs signalent la supériorité théorique de l'autre isotope du phosphore, P^{33}, due à ce que son rayonnement bêta a un trajet plus court dans les tissus.

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ABSORPTION OF COLLOIDAL Au^{198} FROM PERITONEUM AND PLEURA AND ITS INHIBITION BY POLYPHLORETIN PHOSPHATE

by

Bengt Fries and *Gunnar Walinder*

Cancer metastases to the pleura and peritoneum often give rise to effusions in these cavities. Although with our present resources treatment of the primary lesion is as a rule not possible at this stage of the disease, the effusions may still be dealt with. For the past ten years the direct intrapleural and intraperitoneal application of radioactive colloids, especially Au^{198}, has been increasingly accepted as a method of reducing the exudation in the serous cavities.

That colloidal solutions must be used if there is to be any chance of keeping the injected solution in the serous cavity was clear from the outset. Crystalline solutions are absorbed so rapidly that they appear in the blood almost immediately after the injection, and hence no appreciable effect can be expected. Numerous investigations, notably in animals in which the absorption pathways from the peritoneum have been studied (3, 26), have clearly shown that colloidal solutions are chiefly absorbed by the lymphatics and particularly via the cordiform tendon of the diaphragm whence they are further transported, chiefly through the right retrosternal lymph

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duct and only to a lesser extent through the thoracic duct. Colloidal solutions are also absorbed from the pleura via the lymphatics, the amount absorbed, again in this region, being carried away largely via the retrosternal lymph ducts and only to a minor degree through the thoracic duct.

Direct absorption into the blood stream scarcely seems to occur (25). The pleura is devoid of the main drainage pathway for colloidal solutions possessed by the peritoneum in the form of the cordiform tendon of the diaphragm; and this is probably the main reason why solutions of comparable particle size are absorbed much faster from the abdominal cavity than from the pleura, even though other factors, such as the pulmonary and intestinal movements and the nature of the surfaces of the two cavities also affect the absorption rate.

From a comparison of different investigations (3, 26) on the rate of absorption of similar protein solutions from the abdominal and thoracic cavities, it is probably justified to conclude that absorption from the former is approximately four times faster than from the latter.

Radioactive colloidal gold is a favourable agent because of its relatively slow absorption from the cavity into which it has been injected. But from the blood the disappearance of the colloid has been shown to be rapid (13). The radioactivity decreases at first exponentially, being halved in four minutes, and is for the most part absorbed by the liver and spleen.

This form of treatment is based partly upon the direct local effect of the radioactive colloid on the surface of the cavity in question, and partly upon absorption of the gold to the subserous connective tissue. Apart from the indications mentioned, colloidal Au^{198} has been injected locally into tumour foci, *e. g.* in lymph gland metastases in the neck or the pelvis (17, 18, 19). Attempts have also been made to introduce gold via the intestines with the aim of utilizing the absorption of the colloid through phagocytosis and of thus irradiating the regional lymph glands. In Sweden, HULTBORN (9, 10, 11), MELLGREN et coll. (14, 21) have shown that when injected into subcutaneous connective tissues or into mammae, collodial gold is only to a minor extent absorbed or transported to the lymph glands. These observations agree with results earlier communicated in the literature (7, 15).

On the other hand, ALLEN and SHERMAN (23), inter alios, showed in 1950 that colloidal gold, when injected into the parametrium of rabbits and monkeys, was relatively soon absorbed by the regional lymph glands. KOTTMEIER and MOBERGER (12) confirmed these observations and also found comparatively great absorption into the regional lymph glands in patients with carcinoma of the uterine cervix.

A considerable amount of the gold remains, however, in the parametrium. This high uptake is probably due to the good lymph supply in

the parametrium. Similar observations were made by HAHN (8) following the direct injection of colloidal gold into the mediastinum of dogs.

It should be clear from the afore-mentioned that the possibility, on the one hand, of obtaining a more homogeneous local distribution of a radioactive colloid and, on the other, of creating depots would considerably improve the effect of the relevant therapy.

Attempts to arrive at the first-mentioned result were made by KOTTMEIER and MOBERGER in their investigation. For this purpose they used hyaluronidase although they found that the radioactivity in the liver increased at the same time.

Intracavitary gold therapy, however, chiefly aims at a high radioactive content at the site of the injection; this is in order to treat as effectively as possible the carcinosis of the serous membrane that produces the exudation while exposing other organs to the least possible radiation.

The principal aim of the present investigation was to elucidate by means of animal experiments, the rate of absorption into the blood of Au^{198} injected intraperitoneally and intrapleurally and, secondly, to ascertain whether local injection of polyphloretin phosphate, prior to the gold administration, would inhibit absorption of the colloid and thus promote the depot effect desired.

Polyphloretin phosphate (PPP) belongs to a group of compounds of high molecular weight that have been synthesized at the AB Leo Research Laboratories. It is a phosphorylated polyphenol with a molecular weight of about 15,000. Biochemical tests in vitro have shown PPP to be a very active inhibitor of hyaluronidase. In an experimental investigation in animals by one of us (5), it was found that PPP is also biologically active in vivo; local PPP injections into the abdominal cavity of the rabbit to a large extent prevented intraperitoneal adhesions induced by different standardized traumata. The cause of the effect observed was assumed to be that PPP reduced the permeability of the serous membrane which indeed, was found to be the case. Absorption of an intraperitoneally injected protein solution was considerably retarded if the animal had first been treated with PPP, as compared with untreated controls. In vitro experiments on the peritoneal membrane from the rabbit show that this inhibition of absorption occurred because the peritoneum, after treatment with PPP, became less permeable; furthermore the reduction of permeability was not due to the size of the PPP molecule. Extensive tests of this substance have shown its toxicity, both acute and chronic, to be very low. The LD-50 for the mouse and the rat, following intraperitoneal injection, is 600 mg/kg.

On the basis of the above investigation we have sought to ascertain whether the intraperitoneal and intrapleural administration of PPP will inhibit the absorption of a colloidal gold solution subsequently injected.

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On the basis of the above investigation we have sought to ascertain whether the intraperitoneal and intrapleural administration of PPP will inhibit the absorption of a colloidal gold solution subsequently injected.

Method

Autoradiographic examination

Intraperitoneal injection of Au^{198}. The animals chosen for the experiment were mice weighing about 25 g. Twenty-four hours before the injection of gold, half the mice were given 0.5 ml of a 1 per cent PPP solution intraperitoneally, the remaining animals serving as controls. The gold employed was the commercial red colloid with particles of between 20 and 50 mμ. The amount injected was 1 μC. At different intervals after the application of the gold the animals were killed in pairs (one control and one PPP-treated animal). After immersion in carbonic acid-acetone solution at a temperature of about —65° C, the animals were transferred to the refrigeration chamber and sectioned by the tape method of ULLBERG (27), which produces a section of the entire animal. The slices, 20 μ thick, were mounted on Dentus Rapid film (Figs. 1 and 2).

Intrapleural injection of Au^{198}. In this experimental series the animals were mice of the same weight as before. Since the pleural cavity is smaller than the peritoneal, a stronger concentration of PPP was given, only 0.12 ml of a four per cent solution being injected twenty-four hours before the gold administration. In other respects the experimental conditions were the same.

Investigation of radioactivity

For these experiments the animals used were rabbits weighing between 1.7 and 3 kg. Half of them were first given, intraperitoneally or intrapleurally, 100 mg PPP; then — after twenty-four hours — 100 μC Au^{198} per kg was injected into the respective cavities. Blood samples were taken a half to twenty-four hours after the commencement of the experiment, samples of 1 ml being obtained with a heparinized syringe. After twenty-four hours the animals were killed, the livers being removed and the radioactivity in the blood samples and the livers measured (See diagram and table).

The procedure used for the measurements of radioactivity was as follows. The organs were homogenized in aqua regia in identical glass vessels, after which the liver activities were measured in a collimated NaI scintillation counter. The values were compared with a standard solution. Great importance was attached to keeping the geometric conditions identical in connection with the measurements. Thus the levels of the liquid in the glass vessels were exactly the same, as was the placing of the vessels in relation to the scintillation crystal. The blood radioactivities were measured in a 'well-type' NaI crystal and the values compared with a standard solution.

Results

The results of the autoradiographic examinations are presented in Figs. 1 and 2 which show the distribution of the gold at different intervals after its injection into the thoracic and abdominal cavities of the mice. From these figures it is evident that absorption from the peritoneum was very rapid, with high liver activities only a few hours after injection, while at the same time the radioactivity in the abdominal cavity was considerably reduced. The fact that most of the absorbed gold was found in the reticulo-endothelial system, more particularly in the liver and

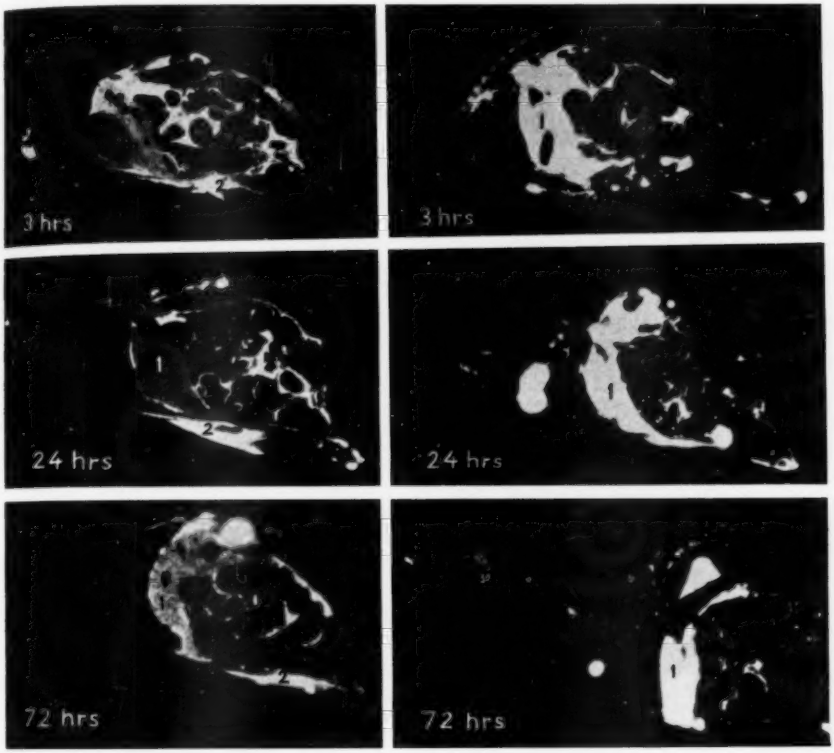


Fig. 1. Autoradiographs of mice, killed at 3, 24, and 72 hours respectively after intraperitoneal injection of Au^{198}. PPP-treated animals to the left, and controls to the right. 1. Liver. 2. Subcutaneous depot of gold not resorbed.

spleen, and to a lesser extent in the bone marrow, accords with previously reported results. FLIEDNER and STODTMEISTER showed (4) that in rats the specific activity in the bone marrow amounted to between 5 and 10 per cent of the specific liver radioactivity.

It should be clear from the above that a quantitative measure of the absorption from the abdominal and thoracic cavities cannot be obtained by determining the liver radioactivity, but that this will convey some idea of the activity in that organ to which the greatest amount of Au^{198} passes, and which thus is especially critical from the viewpoint of radiation damage. Variations in the relation between blood and liver volume as well as numerous other factors, combine to make the hepatic uptake very different in different animals.

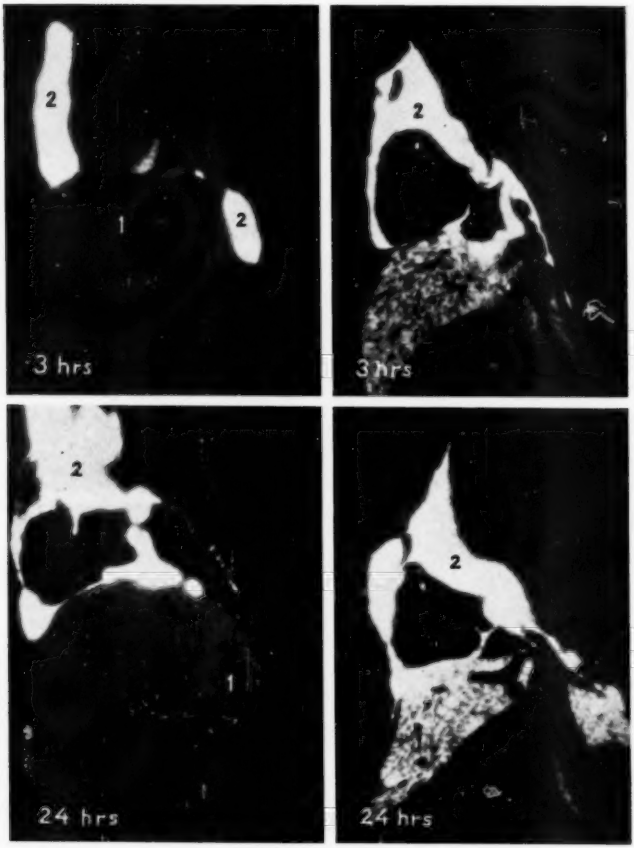
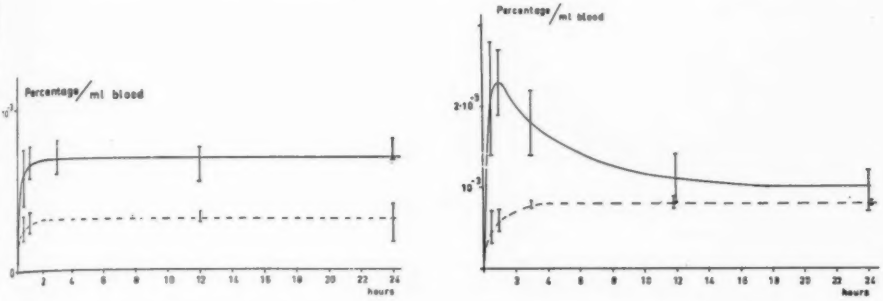


Fig. 2. Autoradiographs of mice, killed at 3 and 24 hours respectively after intrapleural injection of Au^{198}. PPP-treated animals to the left and controls to the right. 1. Liver. 2. Pleural cavity.

A comparison of the two groups represented in Figs. 1 and 2 clearly shows that the ratios of the liver activity/abdominal activity, and, respectively, the liver activity/pleural activity are higher in the controls than in the PPP-treated animals.

The conditions following intrapleural injection were on the whole similar to those observed after intraperitoneal administration, except that in both the PPP-treated animals and the controls the absorption was quantitatively less.



Diagrams 1 and 2. Specific activities in the blood in per cent of the total amount of Au^{198} injected intrapleurally (left) and, respectively, intraperitoneally (right).

Controls: — PPP-treated animals: - - - -.

Tables

Intraperitoneal injections

	Controls				PPP-treated animals			
Activity in blood ..	$(0.7—2.4)\ 10^{-3}$ %/ml				$(0.3—0.8)\ 10^{-3}$ %/ml			
Liver activity	20 %	29 %	20 %	26 %	6.7 %	3.0 %	4.9 %	6.4 %
Weight of animal..	2.3 kg	2.6 kg	1.8 kg	2.2 kg	2.9 kg	2.7 kg	1.9 kg	2.0 kg
Weight of liver ..	70 g	108 g	78 g	80 g	91 g	63 g	65 g	68 g

Intrapleural injections

	Controls			PPP-treated animals		
Activity in blood ..	$(0.4—0.8)\ 10^{-3}$ %/ml			$(0.2—0.4)\ 10^{-3}$ %/ml		
Liver activity	7 %	4.3 %	5.4 %	1.1 %	1.2 %	0.4 %
Weight of animal..	1.7 kg	1.7 kg	1.8 kg	1.7 kg	2.4 kg	1.7 kg
Weight of liver	70 g	77 g	50 g	80 g	110 g	66 g

In the above tables each column represents one animal. The percentages are of the total amount Au^{198} injected.

The measurements of radioactivity in the blood and liver are shown in the Tables above. The findings in rabbits accorded qualitatively with the above-mentioned observations in mice. The effect of PPP seems to have been the same in both the intraperitoneal and the intrapleural cases, inasmuch as the percentage reduction of absorption was equal in each instance.

Blood samples of the animals injected intrapleurally showed that the radioactivity in the blood was fairly constant during the 24 hours subsequent to injection of the gold. After intraperitoneal injection, however, the controls revealed a peak of radioactivity in the blood about one hour after injection. This peak, which was up to about three times the subsequent 'state of equilibrium', could not be found in the animals treated with PPP.

The investigations both in mice and rabbits accordingly suggest that after the intraperitoneal injection of colloidal radioactive gold, the latter is rapidly absorbed from the abdominal cavity, for the most part into the liver. As regards the pleura, the absorption normally is considerably slower; but otherwise the experiments yielded similar results as regards the absorption-retarding effect of PPP.

Even though numerous experiments indicate that, in principle, there is no difference in absorption between different species of animals, the present investigations naturally do not permit any definite conclusions as to the corresponding conditions, especially quantitative ones, in man.

We recently studied a number of cases of ovarian carcinomas in which 100 to 150 mC colloidal gold had been injected into the peritoneal cavity. The stage of the disease varied considerably in these cases. Punctates from the central part of the liver (where the distribution of the colloid is considered homogeneous) and blood samples were taken.

We hope to report in the near future an investigation of the absorption — and its inhibition with PPP — of colloidal Au^{198} from the peritoneum and pleura in human subjects.

SUMMARY

The absorption of colloidal Au^{198} from the pleura and peritoneum into the blood was studied in autoradiographs from whole-body sections of mice and by measurements of blood and liver activity in rabbits. The effect upon the colloid absorption of the direct injection of polyphloretin phosphate into these cavities 24 hours before the injection of gold, was investigated. The absorption of the colloid was reduced in this way to between 10 and 20 per cent of the corresponding absorption in untreated controls.

ZUSAMMENFASSUNG

Die Absorption von kolloidalem Au^{198} aus der Pleura und dem Peritoneum in das Blut wurde an Autoradiographien von Ganzkörperschnitten von Mäusen und mit Hilfe von Messungen der Blut- und Leberaktivität von Kaninchen studiert. Der Einfluss, den eine direkte Injektion von Polyphloretinphosphat in diese Körperhöhlen 24 Stunden vor der Goldinjektion auf die Kolloidabsorption hat, wurde untersucht. Die Absorption des Kolloides wurde auf diese Weise auf 10 bis 20 % der entsprechenden Absorption in unbehandelten Kontrollfällen reduziert.

RÉSUMÉ

Le passage dans le sang de l'or colloïdal Au ^{198} introduit dans la plèvre et dans le péritoine a été étudié sur des souris au moyen d'autoradiographies de coupes du corps entier, et sur des lapins au moyen de mesures de radioactivité du sang et du foie. Les auteurs ont étudié l'effet sur le passage de ce colloïde de l'injection directe de phosphate de polyphlorétine dans ces cavités 24 heures avant l'injection de l'or. Le passage du colloïde est ainsi réduit à 10 à 20 pour cent de son taux chez les témoins non traités.

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MOLLUSCUM PSEUDOCARCINOMATOSUM

by

Folke Linell and *Bror Månsson*

Molluscum pseudocarcinomatosum is a skin tumour resembling squamous epithelial cancer both clinically and histologically, but characterised by a benign course with spontaneous regression. The disease was described in brief in 1936 by McCormac & Scarff in Great Britain under the name of *molluscum sebaceum*. They had observed 10 cases. It was not only the name that roused opposition, but also the description of the lesion as a clinical entity was criticized by many including Savatard who, in 1920, had described such lesions as squamous epithelial cancer in an early stage. Similar cutaneous changes were described by Poth (1939) under the name of 'tumour-like keratoses'.

During the following decade the disease appeared to receive less attention but about 1950 reports of the condition began to appear in the literature. Various names were used: Keratoacanthome (Rook & Whimster 1950), molluscum sebaceum (Dupont 1952), kystes sébacés végétants, verrucomes (Dupont 1952). The literature of the last few years contains a large number of reports of the disease, which has proved fairly common (see references). The somewhat cumbersome name molluscum pseudocarcinomatosum now appears to be the one most widely accepted. As yet neither the nature nor the frequency of the disease has been properly cleared up. In the Scandinavian literature the disease has apparently been referred to on one occasion only and then but briefly (Gentele 1953). It was therefore considered worth while to analyse our

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material which covers a period of 10 years, between 1945 to 1954. Most of the cases had been treated at the Department of Radiotherapy, Lund.

Material. The skin tumours which had been sent to the Department of Pathology in Lund for examination, and there classified as squamous epithelial cancer, squamous epithelial papilloma or atheroma cysts with epithelial proliferation, were re-examined. Most of the specimens molluscum pseudocarcinomatosum were found among those classified as squamous epithelial carcinoma. On the basis of the histologic picture one of us (F. L.) selected the cases suspected of being molluscum pseudocarcinomatosum. A corresponding selection was made by the other (B. M.) on the basis of historical data and the clinical picture. This part of the investigation was considerably facilitated by the fact that photographs were available of most of the skin tumours. All the data collected were afterwards evaluated by both of us, and uncertain cases were rejected. In twenty cases the clinical data strongly suggested molluscum pseudocarcinomatosum, but the biopsy specimens were too small to permit any safe conclusions, and these cases were therefore excluded. A total of 99 cases of molluscum pseudocarcinomatosum, in 95 patients who earlier had been treated at the Department of Radiotherapy between 1945 and 1954, were accepted.

Of the material sent to the Department of Pathology from other hospitals during this 10-year period, clinical data and histologic examination revealed definite molluscum pseudocarcinomatosum in a total of 28 cases.

The total series of molluscum pseudocarcinomatosum in the present investigation thus consists of 127 cases in 123 patients. (Some cases treated after 1954 will be discussed together with the results of treatment.) In the material from the Department of Radiotherapy in Lund there were 67 males and 32 females, which made up a total of 99 out of the 533 cases registered as squamous epithelial carcinoma, *i. e.* about 19 %. In the material from other hospitals there were 19 males and 9 females. Thus, males predominate as in most series on record.

Clinical investigations

Fully developed, a molluscum pseudocarcinomatosum assumes the appearance of a dome-shaped formation in the skin surrounded by normal epidermis. It usually ranges from 10 to 20 mm in diameter and projects like a cupola 5 to 10 mm above the surroundings. Centrally the lesion contains a crater filled with horny masses, sometimes covered by a scale. The covering skin is usually red and shiny (Figs. 1 and 2).

The lesion appears to begin with a rapid proliferation in a small region in an otherwise apparently normal epidermis (HAMPERL). It is fully developed within 3 to 10 weeks. From then on it becomes stationary

and later it gradually begins to regress with shedding of the central horny core. It generally leaves behind a more or less prominent scar varying in size with the degree of any secondary infection. The lesion does not bleed nor does it produce any pain. The patient usually seeks medical advice on cosmetic grounds or because of fear that the rapidly growing tumour might be malignant.

Fig. 1. Typical molluscum pseudocarcinomatosum with cupola-like surface and central crater.

BEARE (1953) pointed out that even scooping out of the central core will hardly produce any bleeding, and he regards this as an almost pathognomonic feature.

Historically molluscum pseudocarcinomatosum differs from squamous epithelial cancer in that it develops relatively rapidly. A molluscum pseudocarcinomatosum may be fully formed within 3 weeks and a history of more than 2 to 3 months is rare. Didactically it has been stated that it takes just as many weeks for a molluscum pseudocarcinomatosum as months for squamous epithelial cancer to reach equal size.

In the present material, the duration of the history was known in all the 99 cases from the Department of Radiotherapy, but in 9 of the other 28 cases from the Department of Pathology, the duration of the history is not known with certainty. The duration of the history, in the 118 cases for which it was known, was less than 6 weeks in 52 cases, 6 to 12 weeks in 47, and more than 12 weeks in 19 cases.

As to the age distribution, the ages of the patients were not known in 3 cases. The age distribution of the other 124 cases is given in Table I.

Inquiry into the family histories revealed no hereditary factors.

The youngest patient was 25 years of age and the oldest 86. The mean age was the same for both sexes. It should be mentioned that the mean age for molluscum pseudocarcinomatosum is about 10 years lower than that found in a large squamous epithelial carcinoma series (MAGNUSSON). To what extent molluscum pseudocarcinomatosum was included in Magnusson's large series is not known.

Fig. 2. Molluscum pseudocarcinomatosum on dorsum of hand. Superficial position in the skin.

Of the 127 patients with molluscum pseudocarcinomatosum, 123

Table I

Age distribution

25—35 years	3	cases
36—45 »	12	»
46—55 »	31	»
56—65 »	35	»
66—75 »	31	»
76—86 »	12	»

Mean age 59.5 years.

had only one lesion. Three (all males) had multiple tumours. One (66 years) had two tumours, one on either side of the nose, at an interval of 6 months, another (67 years) had two tumours, likewise at an interval of 6 months, one behind the ear, the other on the cheek. The third had 3 tumours: the first occurred on the chin when the patient was 38 years old, the second on the right cheek one year later and the third on the left hand 5 years after the first tumour.

As to the localization, molluscum pseudocarcinomatosum shows a predilection for the face and hands (Fig. 3), though it is also known to occur elsewhere, such as in the anal region. In our 127 cases the localization was not found to differ with sex (Table II).

Table II

Localization

	Men	Women	Total
Forehead	2	4	6
Eyelid	5	3	8
Nose	27	13	40
Temple	6	1	7
Cheek	22	13	35
Ear	2		2
Chin	4		4
Neck	2	1	3
Hand	16	6	22
Total	86	41	127

Of the 99 cases treated at the Department of Radiotherapy for squamous epithelial carcinoma most received radiotherapy, and in a few the tumour was excised.

Radiologic treatment consisted in the following methods.

1) Interstitial radium application. Implantation of needles containing 10 mg radium element, active length 8 mm; filtration corresponding to a lead equivalent of 0.9 mm. Minimum single dose 2,500 to 3,000 r/3 1/2 to 4 hours.

2) Fractionated roentgen treatment: 100 kV, 15 mA, H.V.L. 0.1 mm Cu, 4,200 r/6 days to 4,500 r/9 days.

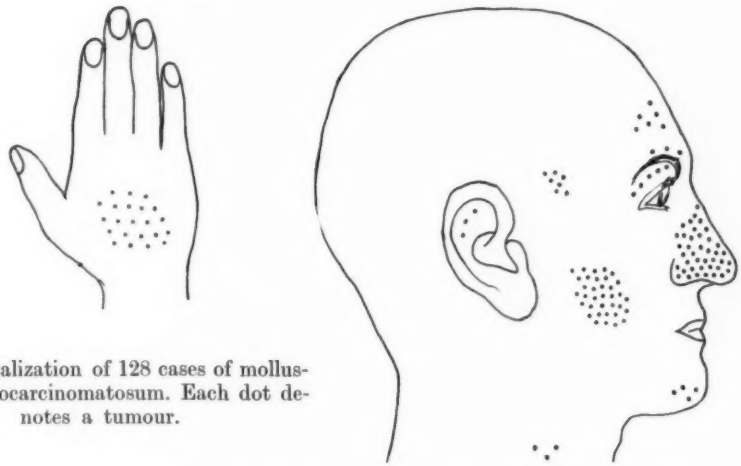

Fig. 3. Localization of 128 cases of molluscum pseudocarcinomatosum. Each dot denotes a tumour.

3) Contact roentgen therapy: 50 kV, 2 mA, F.S.D. 20 or 40 mm. Added filter 0.5 mm Al, H.V.L. 2.7, or 3.8 mm of water. Single dose 6,500 to 7,000 r.

The cosmetic results were satisfactory and scar formation was negligible. No recurrences were seen during the follow-up (2 to 12 years).

In 1954, by when we were on the watch for molluscum pseudocarcinomatosum, clear-cut cases were treated with excision of the exophytic part flush with the surface of the skin, followed by superficial electrocoagulation for stanching any bleeding, and all treated in this way healed satisfactorily. This procedure was also adopted in 14 cases in 1955, and in 12 cases treated between January and September 1956. Of these, 2 recurred and are described later in detail. All the others soon healed satisfactorily.

Histologic studies. The material consisted of blocks embedded in paraffin. Sections 5 μ in thickness were cut and stained as follows: Hematoxylin-eosin, elastica staining with orcein in Fraenkel's modification, melanine staining by silver impregnation according to Masson and staining according to v. Gieson and to Feulgen. In a few instances staining was also performed with phloxin-tartrazin according to Lendrum. For comparison, a case material of 57 clear-cut squamous epithelial cancer of the skin, 5 calcified epithelioma, 19 verrucae, 2 cornu cutaneum and 1 case of Bowen's disease were stained in the same way.

The histologic picture of molluscum pseudocarcinomatosum has been described in detail by earlier workers in this field. Only some diagnostically interesting details will therefore be discussed.

The most striking and important feature is the architecture as a whole with its central horny mass surrounded by squamous epithelium

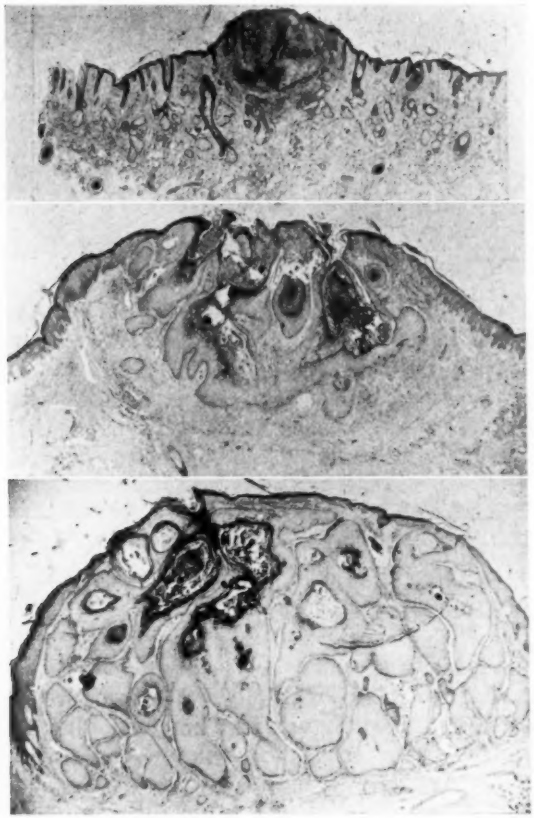

Fig. 4. Series of molluscum pseudocarcinomatosum. *Top:* Small tumour resembling a hypertrophic follicle. *Middle:* Small tumour with a crater filled with horny masses and surrounded by hyperplastic epithelium. *Bottom:* Fully developed tumour with broad epithelial columns growing infiltratively. Note cupola-like shape.

growing symmetrically in all directions in the corium. Growth is usually infiltrative, often in fairly plump columns, though sometimes in thin epithelial streaks. Despite its infiltrative growth the tumour is compact, well circumscribed and lies superficially in the corium. The growth is completed by the dome-like elevation above the surface of the skin, a cupola covered by normal epithelium appearing in sections like a spur with tapering extension over the central crater which is filled with a horny mass.

This description applies to the more or less fully developed lesion.

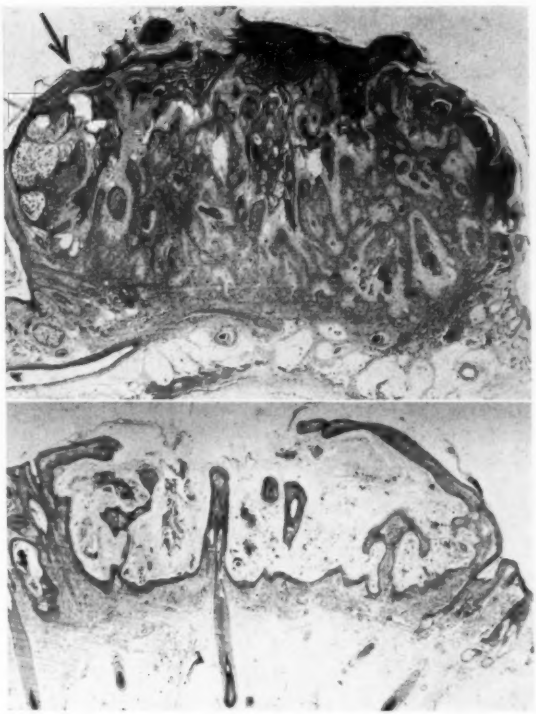

Fig. 5. *Top:* Molluscum pseudocarcinomatosum. Infiltrative growth of epithelium. (Arrow denotes site of epithelial spur.) Tumour situated superficially in the skin. *Bottom:* Molluscum pseudocarcinomatosum in regression consisting of only a cyst filled with horny masses and surrounded by thin atrophic epithelium.

Since the tumour is self-limiting and regresses spontaneously, different stages of development must be considered. Such stages were given schematically by HAMPERL & KALKOFF. In our material we observed pictures fitting in well with this scheme. Fig. 4 shows an early stage, best resembling a monstrous follicle with a central horny core surrounded by proliferating epithelium with a tendency to infiltrate the surroundings. Fig. 5 is probably representative of a late stage which here resembles a horny cyst surrounded by epithelium still sending off a few extensions into the surroundings. Hair-follicles are seen between the rests of the tumour.

Summarizing, it may be said that the histologic picture, especially in the flourishing stage, closely resembles that of highly differentiated

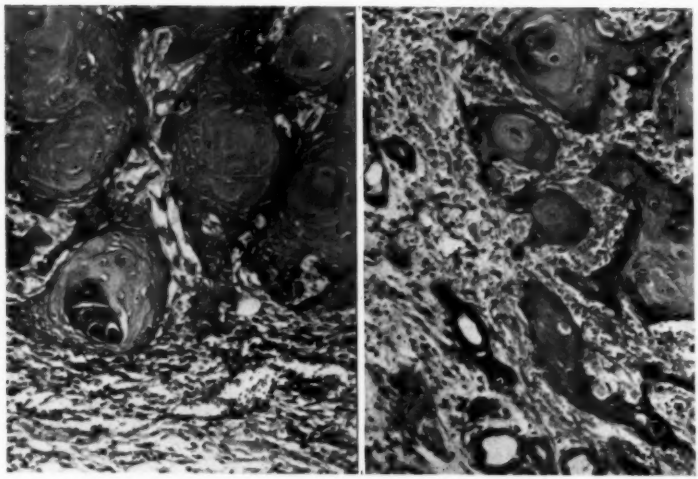

Fig. 6. Two details of molluscum pseudocarcinomatosum. The similarity with differentiated squamous carcinoma is striking.

squamous epithelial cancer (Fig. 6). The earlier confusion is therefore readily understandable. The above-mentioned spur at the edge of the crater is often described as a typical sign of molluscum pseudocarcinomatosum, but it must be borne in mind that in the sections the spur is seen only if the specimen is sectioned vertically through the center of the tumour. Furthermore, this requires complete extirpation of the tumour, or at least a wedged excision in the middle of the tumour. The occurrence of a distinct spur is probably a relatively characteristic feature although not pathognomonic. Spurs were seen in 2 of the 57 cases of squamous epithelial carcinoma; especially in metastases of squamous epithelial carcinoma, which grow from below up into the skin, spurs of this type are seen.

As a rule, molluscum pseudocarcinomatosum is described as resembling highly differentiated squamous epithelial cancer (low grade cancer). Thus, a high degree of keratinization is often found. It has long been known that in squamous epithelial carcinoma keratinization is parakeratotic and that normal hornification with the formation of keratohyaline granules is rare (observed in only 3 of the 57 carcinomas of our material). Parakeratosis is also seen in molluscum pseudocarcinomatosum, but in addition more or less widespread hornification of normal type is common. The relative proportion of the two types of hornification varies widely; in the later stages hornification may be normal throughout.

The high degree of differentiation in molluscum pseudocarcinomatosum also manifests itself in usually distinct prominent differentiation zones in the epithelial columns. The non-keratinised cells are as a rule large and pale, *i. e.*, they take on only little of the ordinary stains. The nuclei also stain only faintly. The paleness of the epithelial columns is almost always striking, especially in comparison with surrounding normal epithelium (Fig. 7). As a rule, it is only the outermost layer in the epithelial columns that has cells with more basophilic cytoplasm (Fig. 8). The nuclei are as a rule very large, vesicular and contain one or more large, usually eosinophilic nucleoli. In addition, the absence of marked atypia and cell polymorphism is a prominent feature. Staining according to Feulgen gave only little additional information as compared with ordinary hematoxylin-eosin staining (Fig. 8), but the pale epithelial columns contrasted well against the more strongly stained nuclei in the surrounding epithelium. As a rule, only the outermost layer of the cells in the tumour columns had deep-stained nuclei. In the cancer cases, on the other hand, dark and pale-stained nuclei were seen intermingled in the centres of the cell columns without ordinary layers of more or less differentiated cells.

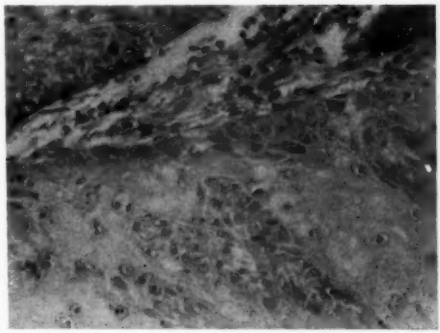

Fig. 7. Top left hand corner, normal epithelium, and below, epithelium in molluscum pseudocarcinomatosum. Poor stainability.

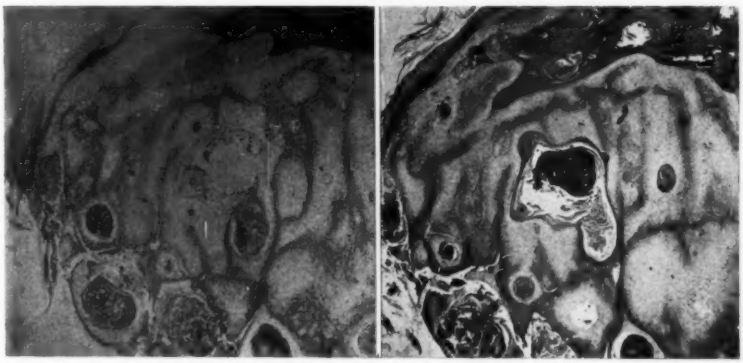

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Fig. 8. Molluscum pseudocarcinomatosum. a) Feulgen staining. b) Staining with hematoxylin-eosin. Regular intensity of stain in most peripheral zones of epithelial columns.

As might be expected in a formation of limited development, the frequency of mitoses in molluscum pseudocarcinomatosum varies widely. Sometimes numerous mitoses were seen and no definite difference could be found between true carcinoma and molluscum pseudocarcinomatosum with regard to mitotic frequency, at least not in the flourishing stages of the latter.

In view of the suggestion put forth by some authors that molluscum pseudocarcinomatosum might be of virus origin, a careful search was made for inclusion bodies, but like earlier investigators we were unable to find any.

For the occurrence of melanine pigment we studied sections impregnated with silver according to Masson. In none of the 57 squamous epithelial carcinomas was any pigment demonstrated in the tumour epithelium. This is in agreement with the results of LENNOX (1949). (In his excellent paper LENNOX depicts the disappearance of melanine in a squamous carcinoma (Fig. 8). We think that he now would have diagnosed this tumour as a case of molluscum pseudocarcinomatosum (BAUMANN & LENNOX 1954).)

In most cases of molluscum pseudocarcinomatosum the epithelium was free from pigment but small amounts of melanine were found in 24 cases (about 20 per cent). It was always localized basally in the epithelium, and occurred in markedly dendritic cells resembling melanoblasts (Fig. 9). The pigment was often only seen in patches in the tumour epithelium. As a rule pigment was found in the lesion only when the surrounding skin was richly pigmented. The pigment in the surrounding skin decreased rapidly or disappeared altogether a short distance from the tumour (Fig. 10). It is usually claimed that, contrary to what occurs

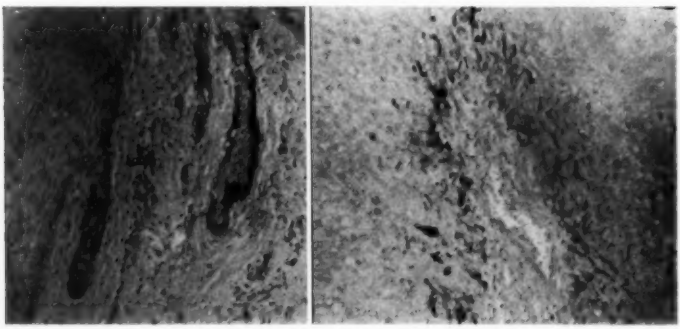

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Fig. 9. Silver impregnation according to Masson of melanotic pigment. a) Normal surrounding epithelium. b) Epithelial columns in molluscum pseudocarcinomatosum. Pigment regularly accumulated in dendritic cells in basal layer.

Fig. 10. Molluscum pseudocarcinomatosum. Silver impregnation, according to Masson, of melanotic pigment. Tumour epithelium completely free from pigment, and in the surrounding epithelium it decreases in direction towards the tumour.

in carcinoma, epithelial atypia is not seen in the adjacent skin, but in our material impregnation of the pigment showed changes in the epithelium in the immediate neighbourhood of the tumour.

It has often been reported that the stroma usually contains numerous inflammatory cells, even more than in carcinoma. Although this is probably correct, it should be pointed out that in flourishing early stages of molluscum pseudocarcinomatosum, the reaction of the stroma may be slight. In the later stages, the occurrence of abundant round cells and leucocytes is the rule. Granulomas with histiocytes and giant cells are not uncommon. But this is also found in genuine carcinoma and therefore is of no definite differential diagnostic value. Infiltrative and destructive-growing carcinoma as a rule destroy the elastic fibres of the corium, and usually most of the orcein stainable substance in the stroma is lost in a squamous epithelial carcinoma. In molluscum pseudocarcinomatosum many elastic fibres survive between the epithelial columns. This, however, provides no definite mark of distinction between this condition and genuine carcinoma because in some cancer cases a number of elastic fibres survive at the base, or between the epithelial columns.

Discussion

The problem at present outranking all others is the diagnosis, since it can now be regarded as established that molluscum pseudocarcinomatosum is a special, benign tumour. It appears that as yet no reliable diagnostic criteria are available to distinguish it from squamous epithelial carcinoma. This is *a priori* also understandable as transitions between hyperplastic conditions and carcinoma exist. Some authors have claimed to have verified a diagnosis of molluscum pseudocarcinomatosum histologically. In our opinion such verification is not possible, and after the study of our fairly large material we would rather adhere to the opinion of HAMPERL & KALKOFF, for example, who stated that the diagnosis

is as a rule only possible on the basis of a careful analysis of the clinical data in combination with the microscopic findings. As to the histologic appearances it must be emphasized that as yet no specific characteristics of molluscum pseudocarcinomatosum are known. The following features may be regarded as diagnostically important:

1. The architecture as a whole. 2. The high degree of differentiation. 3. The poor stainability of the tumour columns. 4. The marked reaction of the stroma, especially in the later stages. 5. Preserved elastic fibres in the stroma. 6. Normal hornification with kerato-hyaline granules. 7. The occurrence of regular layers of pigment in the tumour-columns argue against carcinoma.

The most important feature in our opinion are the appearances as a whole. Consequently it is important for the pathologist to receive relatively large biopsy specimens, preferably the entire tumour. If the latter be cut flush with the surface of the skin, the specimen will include the bulk of the growth, and the pathologist can then examine it in vertical sections through its centre. It is probably no exaggeration to state that the diagnosis of squamous epithelial carcinoma is relatively often poor because the material is too scanty or the fragments too small. The fear of missing malignant tumours may then lead to 'overdiagnosis'. If the pathologist finds infiltrating squamous epithelial columns in small pieces of tissue, he may make at least a provisional diagnosis of squamous epithelial carcinoma even if the degree of maturity of the epithelium is high. For this reason and because of inadequate knowledge of molluscum pseudocarcinomatosum, most series of squamous epithelial carcinoma have probably contained a number of cases of the former.

In this material, 19 % of the cases were molluscum pseudocarcinomatosum. This percentage is a minimum figure. It is stated in the literature that one third to one fourth of cases treated earlier as squamous epithelial carcinoma were in reality molluscum pseudocarcinomatosum (Beare 1953). Thus the frequency of the condition in southern Sweden appears to be about the same as that found by other investigators in other parts of the world.

Earlier, when molluscum pseudocarcinomatosum was diagnosed as squamous epithelial carcinoma or inverted papilloma, treatment was either surgical or radiologic.

Untreated molluscum pseudocarcinomatosum runs the typical course described above; this, from its clinical appearance until regression and disappearance, takes between 6 months and 1 year. Often, though not always, the clinical picture is so distinct that one may very well refrain from active therapy. Histologic examination is as desirable, however, as is active intervention (from a cosmetic point of view) because spontaneous healing often leaves behind ugly scars.

Surgery has been used with success. Radical excision has produced both rapid healing and sufficient material for histologic examination. Rapid healing and satisfactory cosmetic results have also been obtained by such methods as diathermy coagulation, freezing with ethyl chloride with subsequent curettage of the central cavity, and freezing with carbon dioxide snow as the only measure.

BEARE (1953) stressed that the best healing results were obtained by cutting off the tumour flush with the skin and subsequent superficial electrocoagulation to control hemorrhage. In the beginning he also gave roentgen therapy of 800 to 1,200 r, but since it did not accelerate resorption, it was afterwards abandoned.

FINNEY (1954) tried to estimate the optimal dose for roentgen therapy. He used uniform radiation conditions (60 kV, 4 mA and H.V.L. 3.3 mm Al). The treatment was given as a single exposure but in varying dosage. The area treated was inspected weekly or fortnightly to assess the degree of reaction and the rate of regression. The doses varied between 1,250 and 2,500 r. The most suitable dose was found to lie between 1,500 and 1,750 r; it gave the most rapid healing and moderate radiation reaction.

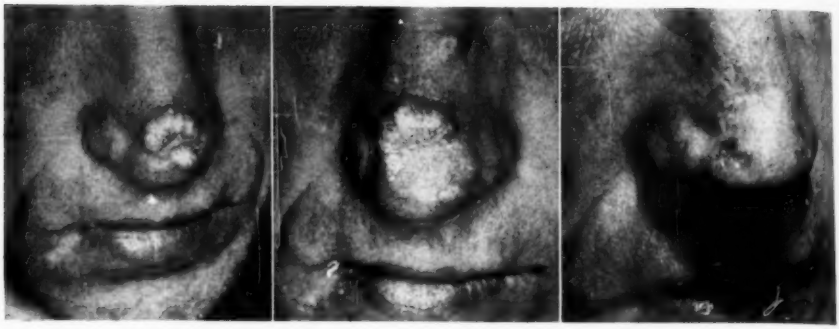
BEARE (1954) likened radiotherapy of molluscum pseudocarcinomatosum to 'using a sledge-hammer to drive in a nail'. This opinion is, however, not shared by all, and HALNAN (1953—1954) claims that the changes should be treated with respect either by radical excision or by adequate radiation as if in the nature of squamous epithelial carcinoma, because according to him there are border-line cases which cannot be distinguished with certainty from genuine carcinoma.

Our attitude is as follows. If the diagnosis is certain, *i. e.* if both the clinical and histologic pictures indicate molluscum pseudocarcinomatosum, the tumour may with advantage be cut off flush with the skin. Doubtful cases, in which malignancy cannot be excluded, should be treated as carcinoma.

BEARE (1953) described a case in which curettage of an apparently typical molluscum pseudocarcinomatosum was followed by rapid growth. It was therefore treated, like a similar case (CHURCH 1955), with radiotherapy. SIMPSON (1955) also described a case in which after curettage recurrence was observed after an interval of 3 weeks. Later, however, spontaneous healing occurred within 6 weeks.

At the Department of Radiotherapy one case was treated in 1955 and another in 1956 with recurrences after section flush with the skin and electrocoagulation. These cases are not included in the material referred to above.

Case 1. Male, aged 71. Caretaker. A typical molluscum pseudocarcinomatosum had developed during the previous 3 weeks and on admission was 12 mm in diameter and had a central horny core. Histologic examination also presented a characteristic



a b c

Fig. 11. a) Molluscum pseudocarcinomatosum of nose. The groove across the tumour is due to earlier excision of a biopsy specimen. b) Recurrence after cutting off tumour flush with skin. Base of tumour larger than previously. In addition, small new tumour on bridge of nose. c) Healed after re-excision.

picture and the lesion was excised; it recurred and one month later was 25 mm in diameter and had a central necrotic core. The growth was again cut off flush with the skin and histologic examination gave the same result as earlier. After a further 6 weeks the growth again progressed and was excised for the third time. Histologic examination showed the same picture as before. Six weeks later the lesion had healed completely leaving behind a pale scar which had the same appearance when seen 9 months later.

Case 2. Male, aged 55. Farm labourer. Growth on tip of nose for about 6 weeks. Treatment with electrocoagulation elsewhere. The growth did not heal and he was referred to the Department of Radiotherapy. The lesion measured 18 mm in diameter and had a central pit (Fig. 11).

The tumour was cut flush with the surface and histologic examination showed a pale-celled squamous epithelium well demarcated against the underlying tissue. The changes were interpreted as molluscum pseudocarcinomatosum. One month later the growth had again increased in size and in addition there was a similar lesion measuring 5 × 6 mm at the root of the nose and 2 cm from the original lesion (Fig. 11). Both lesions were cut flush with the skin. Histologic examination of material from the lesions showed appearances of molluscum pseudocarcinomatosum. Three weeks later the smaller lesion had healed while the larger one had proliferated within a 4 × 4 mm region. The patient had 2 more recurrences, one 3 weeks after the other. Histologic examination of these tumours showed the same picture as before.

The large lesion thus recurred 4 times. When last seen, 8 months after the first treatment: no signs of a recurrence and the cosmetic effect satisfactory. On all 4 occasions the same histologic appearances with highly differentiated epithelium without signs of malignancy, were noted.

Cases which recurred after extirpation were regarded by earlier authors as having been erroneously diagnosed and therefore afterwards treated as if they were squamous epithelial carcinoma. The 2 cases now

reported show that molluscum pseudocarcinomatosum can very well recur several times and nevertheless later turn out to be benign.

In our series molluscum pseudocarcinomatosum had the same localization as most squamous epithelial carcinomas. This might suggest an exogenic origin. Inclusion bodies have never been demonstrated and the few inoculation experiments that have been carried out (BEARE) have been negative. The localization might possibly be due to exogenic effects, such as ultraviolet light, paving the way for the development of molluscum pseudocarcinomatosum. It might be mentioned that the tumour-like keratoses described by POTH, and which seem to be closely related to molluscum pseudocarcinomatosum, occurred in those regions of the skin exposed to intense insolation. In our material the time of development of the tumour was evenly distributed throughout the year.

A question of importance is whether molluscum pseudocarcinomatosum is in any way related to squamous epithelial carcinoma. The fact that none of our patients subsequently developed the latter might argue against such relationship. HAMPERL & KALKOFF have stressed the recognised similar behaviour of molluscum pseudocarcinomatosum and the tumours produced in the skin of rabbits by tar or carcinogenic hydrocarbons. These tumours, called carcinomatoids by ROUS et coll. regress spontaneously as soon as the effect of the carcinogenic agent wears off. On continued treatment they will, however, sometimes develop to metastasising carcinoma (BERENBLUM, LINELL & NORDEN). These experimental investigations do not, however, permit any valid conclusions on the biologic nature of molluscum pseudocarcinomatosum in man.

Earlier investigators have discussed the possibility of a relationship between molluscum pseudocarcinomatosum and so-called multiple self-healing squamous carcinoma. The latter, described by FERGUSON-SMITH 1934 and later reported in a number of cases, is characterised by its familial occurrence and by a large number of skin tumours. The individual tumours can in some respects obviously closely resemble molluscum pseudocarcinomatosum both macro- and microscopically. We have not had the opportunity of seeing any carcinomas of this kind but none of our cases of molluscum pseudocarcinomatosum appeared to be familial. Multiplicity was observed 3 times with 3 tumours in one and the same person, but even then only one tumour was seen at a time; the interval between the appearance of the tumours varied between six months and four years. Thus no transitions were observed between multiple self-healing squamous carcinoma and molluscum pseudocarcinomatosum and we are therefore inclined to regard them as separate clinical entities. As to the co-existence of molluscum pseudocarcinomatosum and carcinoma, it might be mentioned that of the 99 patients treated at the Department of Radiotherapy 7 had earlier been treated for cancer; of

these 1 had cancer of the uterine cervix, 1 of the mammary gland, 1 had squamous epithelial cancer of the skin, and 4 basal cell carcinoma. In view of the relatively high frequency of these conditions as well as of molluscum pseudocarcinomatosum, their co-existence in a certain percentage of patients can be ascribed to chance.

SUMMARY

A material of 127 cases of molluscum pseudocarcinomatosum in 123 patients is discussed. About 20 per cent of tumours, formerly diagnosed as cutaneous squamous epithelial carcinoma turned out to be molluscum pseudocarcinomatosum. The mean age was 59.5 years, about 10 years lower than in cases of squamous epithelial carcinoma. The lesion was localized exclusively to the face and hands. In 3 cases multiple tumours were seen. The histologic picture is described and it is stressed that the specimen collected for pathologic examination should preferably consist of the entire tumour, although this may often not permit a diagnosis without supplementary clinical data. In cases with a definite diagnosis it is recommended that the tumour be cut off flush with the skin. Uncertain cases are best treated as carcinoma.

ZUSAMMENFASSUNG

Ein Material von 127 Fällen von Molluscum pseudocarcinomatosum bei 123 Patienten wird diskutiert. Etwa 20 % der Tumoren, die früher als Stachelzellenkrebse der Haut diagnostiziert worden sind, erwiesen sich als Molluscum pseudocarcinomatosum. Das Durchschnittsalter war 59.5 Jahre, etwa 10 Jahre niedriger als in Fällen mit Stachelzellenkarzinom. Die Erkrankung kam ausschliesslich im Gesicht und auf den Händen vor. In 3 Fällen wurden multiple Tumoren beobachtet. Das histologische Bild wird beschrieben und es wird betont, dass die zur pathologisch-anatomischen Untersuchung ausgewählten Präparate vorzugsweise aus dem ganzen Tumor bestehen sollten, obwohl dieses oftmals die Diagnosestellung ohne ergänzende klinische Daten nicht gestattet. In Fällen mit definitiver Diagnose wird empfohlen, den Tumor in Hauthöhe abzuschneiden. Unsichere Fälle werden am besten wie Karzinome behandelt.

RÉSUMÉ

Les auteurs analysent une série de 127 cas de molluscum pseudocarcinomatosum observés chez 123 malades. Environ 20 pour cent de ces tumeurs, primitivement diagnostiquées comme des épithéliomas malpighiens cutanés, se sont révélées être des molluscum pseudocarcinomatosum. L'age moyen était de 59.5 ans, inférieur d'environ 10 ans à celui des cas d'épithélioma malpighien. Cette lésion était localisée exclusivement à la face et aux mains. Dans trois cas on a observé des tumeurs multiples. Les auteurs en décrivent les caractères histologiques; ils soulignent que la pièce prélevée pour l'examen anatomo-pathologique devrait, de préférence, comprendre la tumeur en entier, bien que ceci ne permette souvent pas un diagnostic sans données cliniques complémentaires. Quand le diagnostic est établi avec certitude, il est recommandé d'enlever la tumeur au ras de la peau. Il vaut mieux traiter les cas douteux comme des épithéliomas.

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ACTION DE LA CYSTAMINE PER OS SUR LA SURVIE DES SOURIS IRRADIÉES PAR LE RADIOCOBALT 60

par

D. J. Mewissen

Depuis le travail original de Bacq et collaborateurs (2), la cystamine (disulfure de β-mercaptoéthylamine, disulfure de Becaptan) a fait l'objet de plusieures études qui ont confirmé ses propriétés radioprotectrices (5, 6). Ce protecteur chimique contre les radiations présente deux avantages appréciables. Il est actif par voie orale et son activité est de longue durée: encore appréciable 4 à 5 heures après administration (7, 8). Ces propriétés ont été généralement mises en évidence par l'observation de la mortalité chez des souris ou des rats, soumis à une irradiation totale par une dose unique de rayons roentgen.

Il nous a paru intéressant d'étudier l'action de la cystamine *per os*, dans le cas d'une irradiation totale par doses fractionnées de rayons gamma, à faible intensité (13 r/min) et durant des temps d'exposition relativement longs (de 11 à 28 minutes). En effet, ces modalités d'irradiation sont susceptibles d'être observées en pratique chez l'homme. En temps de paix, le personnel technique des installations nucléaires, voire même la population du voisinage, peuvent être exposés, pendant des durées de temps variables, à des rayons gamma, en dose unique ou multiple. En cas de guerre, les armées, les formations de la Sécurité Civile et les populations peuvent être irradiées dans des conditions similaires à la suite d'explosions nucléaires ou de retombées radioactives.

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Matériel et méthodes. Ce travail a été entrepris en vue d'obtenir des résultats qualitativement et quantitativement significatifs. ELLINGER a récemment attiré l'attention (17) sur l'importance de certains facteurs physiques et biologiques. BACQ a insisté (3) sur l'importance d'un contrôle statistique rigoureux dans les expériences de protection utilisant la mortalité comme critère. Le plan de l'expérimentation a été établi pour permettre l'analyse des résultats par la méthode des probits (18).

Nous avons utilisé, au total, 355 souris C57Bl., subline 6, mâles et femelles, âgées de 38 ± 3 jours et d'un poids moyen de 13.0 gr (En provenance de Roscoe B. Jackson Memorial Laboratory, Bar Harbor, Maine, U. S. A.). La cystamine (L 1591 Labaz) obtenue en poudre, a été diluée à la concentration de 25 mg/cc dans du sérum physiologique, immédiatement avant utilisation. L'administration à la souris a été faite par tubage gastrique, au moyen d'une petite canule en argent, à la dose de 4 mgr/10 gr, 20 minutes avant l'irradiation.

Les souris-contrôles irradiées reçurent, dans les mêmes conditions, du sérum physiologique par intubation. Les animaux furent répartis par groupes de 12, dans 8 séries de traitement. A cause des petits écarts inévitables de doses reçues par des souris de groupes différents et pour minimiser leur influence dans la comparaison des animaux traités et non traités par la cystamine, les dispositions suivantes ont été prises:

1. Chaque groupe irradié se composait d'un nombre égal de souris-contrôles ayant reçu du sérum physiologique et de souris traitées par la cystéamine.

2. Les souris ont été irradiées dans un container cylindrique perforé, en lucite, mesurant 20 cm de diamètre et 3.5 cm de haut, divisé en 12 compartiments radiaux égaux. Ce container est en rotation autour de son axe vertical, dans le faisceau radiant, à la vitesse d'un tour par minute.

3. Chaque souris fut placée dans son compartiment individuel, la tête tournée vers le centre de rotation et resta dans cette position durant toute l'exposition.

4. Quand le groupe irradié ne comprenait pas 12 animaux, les compartiments libres furent occupés par des fantômes de bois (6 × 2 × 2 cm) en vue de limiter l'erreur due au side-scatter (17).

Un appareil de téléthérapie au Cobalt 60, d'une puissance d'une hectocurie, a été utilisé comme source radifère avec les facteurs physiques d'irradiation suivants: distance source—objet 60 cm, intensité 13.1 r/min.

Les mesures d'intensité ont été faites au moyen d'une chambre-dé Victoreen à condensateur, logée dans le container d'irradiation en rotation dans le faisceau de rayonnement. La moyenne de 3 déterminations fut 13.1 r/min. Des mesures complémentaires ont été effectuées par dosimétrie au sulfate ferreux. (Nous remercions R. L. HAYES, Medical Division, Oak Ridge Institute of Nuclear Studies, Oak Ridge, Tennessee, U. S. A.) La moyenne de 3 déterminations fut 13.2 r/min.

Les 8 groupes de traitement ont reçu 4 doses totales différentes selon une échelle progressive, chaque dose étant égale au produit de $e^{0.3}$ ($\simeq 1.35$) par la dose immédiatement inférieure. Ces doses totales furent administrées en deux fractions égales, à 5 jours d'intervalle. La cystamine ou le sérum physiologique ont été donnés 20 minutes avant chaque exposition. Quelques animaux-contrôles non irradiés ont reçu de la même manière de la cystamine par intubation en vue d'exclure la possibilité d'une mortalité propre à ce procédé.

Les souris ont été gardées à température constante, dans des cages de fer, par groupe de 4, avec nourriture Purina chow et eau à volonté. Toutes les souris qui moururent endéans les 30 jours qui suivirent la première irradiation furent systématiquement autopsiées et les organes représentatifs soumis à l'examen microscopique.

Tableau 1

Dose totale	Durée d'exposition	Nombre initial de souris	Nombre de morts après 30 jours	Mortalité
Serum physiologique				
301 r	11 min 30 sec	40	14	35
406 r	15 min 30 sec	50	24	48
550 r	21 min	63	34	55
742 r	28 min 20 sec	60	47	78
Cystamine				
301 r	11 min 30 sec	16	4	25
406 r	15 min 30 sec	24	9	35
550 r	21 min	62	28	45
742 r	28 min 20 sec	28	17	61
	Contrôles non irradiés	12	12	0

Résultats expérimentaux

Les relevés de mortalité aux quatre différents niveaux d'irradiation, chez les souris-contrôles et chez les souris traitées par la cystamine sont rassemblées dans le Tableau 1.

La répartition des morts dans l'intervalle de 30 jours suivant la première irradiation est indiquée pour les 8 groupes de traitement dans le Tableau 2.

La distribution de fréquence de mortalité dans les différents groupes peut être caractérisée comme suit:

1. A dose égale, le taux de mortalité est plus bas chez les souris traitées à la cystamine.

2. Le centre de distribution de la mortalité dans le temps s'éloigne d'autant plus de l'origine que la dose totale est plus faible.

3. A dose égale, le centre de distribution est plus éloigné de l'origine dans le groupe cystamine comparé au groupe contrôle.

La D. L. 50/30 jours a été estimée pour le groupe-contrôle et pour le groupe traité par la cystamine.

Les probits expérimentaux sont obtenus à partir des pourcentages rassemblés dans le tableau 1 et les lignes de régression sont ajustées par la méthode de vraisemblance maxima (Diagramme 1) (18). Voici les équations de régression obtenues:

a) groupe contrôle:

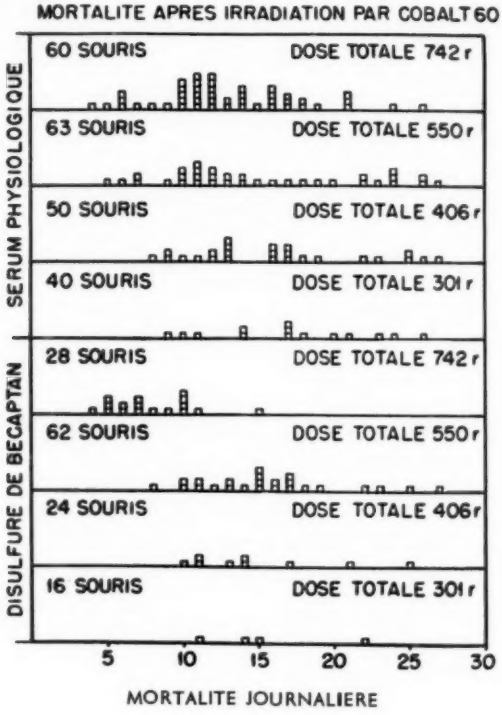
$$Y = -2.70 + 2.94\ x$$

b) groupe cystamine:

$$Y = -1.71 + 2.42\ x$$

Tableau 2

Distribution de la mortalité aux quatre différents niveaux d'irradiation chez les souris contrôles et chez les souris ayant reçu de la cystamine per os



La variable indépendante x représente le «dosage» c'est à dire le logarithme de la dose totale en r. En substituant dans les équations (1) et (2), x par la valeur d'un dosage considéré, on obtient la valeur Y du probit de mortalité correspondant. L'estimée de vraisemblance maxima $\overline{m}$ est la valeur de x quand $Y = 5.0$ (50 % de mortalité). La valeur de la D. L. 50/30 jours est donnée par l'antilogarithme de $\overline{m}$ et à partir de $V_{\overline{m}} = \frac{1}{b^2}\left\{\frac{1}{Snw} + \frac{(\overline{m} - \overline{x})^2}{Snw(x - \overline{x})^2}\right\}$ (variance de l'estimée de vraisemblance maxima) se calculent les limites fiduciaires au seuil de probabilité de 95 %. Le test de χ^2 de PEARSON montre que dans les deux groupes, il n'y a pas d'hétérogénéité entre les probits expérimentaux et les valeurs de la ligne de régression ajustée.

Voici les D. L. 50/30 jours estimées:

a) groupe contrôle:

$\overline{m} = 2.619$; antilog. $\overline{m}$: **416 r.**

$V_{\overline{m}} = 0.001537$; limites fiduciaires: **380 r et 455 r.**

b) groupe cystamine:

$\overline{m} = 2.776$; antilog. $\overline{m}$: **597 r.**

$V_{\overline{m}} = 0.002619$; limites fiduciaires: **531 r et 672 r.**

Par conséquent, on peut estimer avec une probabilité fiduciaire de 95 %, que la valeur réelle de la D. L. 50/30 jours est comprise entre 380 r et 455 r pour le groupe-contrôle et entre 531 r et 672 r pour le groupe cystamine.

Le degré de protection obtenu par la cystamine contre la mort par radiation est donc statistiquement significatif dans les conditions d'expériences.

Discussion des résultats

Notre estimation de la D. L. 50/30 jours est inférieure à celle obtenue pour différentes races pures de souris (19). Nous ne pouvons a priori exclure une radiosensibilité particulière de la subline 6 des C57B1. D'autres facteurs sont à considérer, dont l'influence a été discutée ailleurs (21). L'âge des souris utilisées (38 ± 3 jours) semble avoir été le facteur critique responsable (1).

Il est intéressant de comparer les résultats obtenus dans la protection par la cystéamine avec ceux présentés ici pour la cystamine. Pour ce motif, nous reproduisons le graphique de régression que nous avons obtenu (21) pour la cystéamine (Diagramme 2). De la comparaison des

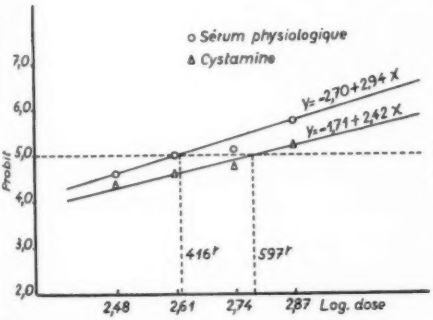


Diagramme 1. Droites de régression des probits pour le groupe contrôle et pour le groupe cystamine.

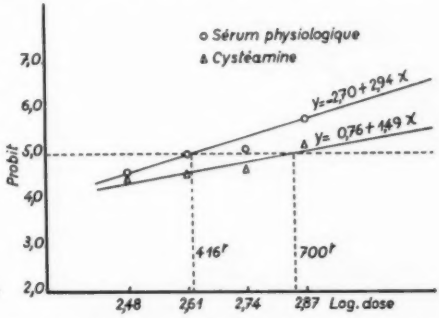


Diagramme 2. Droites de régression des probits pour le groupe contrôle et pour le groupe cystéamine.

lignes de régression respectives, on déduit que, dans nos conditions expérimentales, la cystéamine est légèrement plus active dans la protection contre l'effet létal des rayons gamma.

Le D. R. F. (dose reduction factor) est 1.68 pour la cystéamine et 1.43 pour la cystamine; ces chiffres ne sont pas une mesure absolue de l'effet protecteur, au stade initial de la chaine de réactions qui va du transfert d'énergie à l'effet biologique observable. Le fractionnement de la dose modifie les mécanismes de la mort par radiation de telle sorte que l'efficacité des protecteurs chimiques semble diminuée (21). Le D. R. F. est de préférence évalué après une dose unique. Dans ces conditions, il a été estimé à 2 environ pour la cystéamine (4, 24); pour la cystamine il serait légèrement supérieur (2, 3). L'effet réducteur de dose a été estimé à 40 % pour la cystéamine (25), ce qui correspond à un D. R. F. d'environ 1.67.

Une constatation nous paraît digne d'interét. Les lignes de régression du groupe contrôle et du groupe protégé forment un angle ouvert à droite, tant dans le cas de la cystéamine que dans celui de la cystamine. Notons que la même particularité a été observée dans nos expériences de protection contre le radio-phosphore administré par voie interne. La cystamine donnée *per os* à des souris, pendant 30 jours, diminue l'effet létal du P^{32} injecté par voie intrapéritonéale (22). Une explication possible de ce phénomène est que la courbe dose-réponse de mortalité soit la résultante de deux composantes, ou plus. Nous savons d'ailleurs que la pathogénèse de la mort par radiation ressortit à plusieurs mécanismes complexes (14, 9). Dans ce cas, la ligne de régression n'est plus une droite et l'ajustement par la méthode de vraisemblance maxima est fondamentalement une approximation. Considérons le cas le plus simple de deux composantes identifiables, l'une dont l'influence sur la mortalité est prépondérante aux doses inférieures choisies, l'autre aux doses supérieures. Les pentes respectives des lignes de régression formeront un angle ouvert à droite si l'effet protecteur est plus marqué sur la deuxième composante que sur la première. En conséquence, le degré de protection et la valeur du D. R. F. augmenteront avec des doses totales croissantes, du moins entre certaines limites.

En fait, l'étude statistique de résultats obtenus avec la cystéamine nous a conduit à postuler (21) que l'effet létal des rayons gamma est statistiquement assimilable à l'action conjointe indépendante (selon FINNEY (18), 'Joint independent action,) de deux composantes (Diagramme 3). Dans la première, l'organe critique parait être l'intestin. L'action protectrice de la cystéamine est modérée. La physiopathologie de l'intestin irradié est en effet complexe (13); des mécanismes directs et indirects déterminent sa réponse à l'irradiation. Il est certain que la protection chimique accélère sa restauration histologique (12, 20). DE-

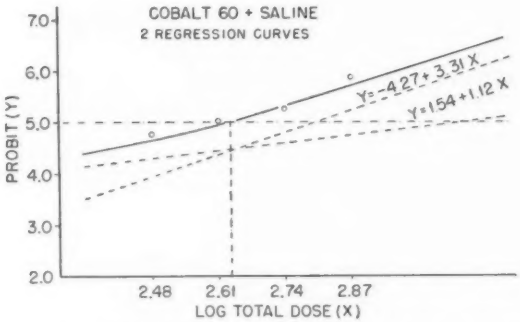


Diagramme 3. Analyse de l'action indépendante de deux phases de mortalité observées chez des souris non protégées, chacune avec une droite de régression des probits (pointillés). La courbe résultante (trait plein) est calculée à partir des deux composantes

SAIVE a montré que la cystéamine protège l'intestin de rat contre une irradiation locale de 500 r et par tabulation des différentes phases mitotiques, son action est mise en évidence dès la 12e heure (15). L'organe critique de la seconde composante est la moelle osseuse qui est protégée à un haut degré, probablement parce qu'elle concentre la cystéamine (et la cystamine) (16).

Les graphiques de régression obtenus pour la cystamine sont très voisins de ceux obtenus pour la cystéamine. Il est donc possible que les mêmes phénomènes soient dans les deux cas responsables de l'augmentation du D. R. F. avec les doses croissantes expérimentales. Le quotient des coefficients de régression du groupe protégé et du groupe contrôle mesure le facteur d'accroissement du D. R. F. en fonction de la dose. A partir de nos résultats, il est 1.9 pour la cystéamine et 1.2 pour la cystamine (Diagramme 1, Tableau 3).

Tableau 3

Coefficients de régression

	Groupe contrôle	Groupe protégé	Rapport
Rayons gamma Co^{60} + Cystéamine ..	2.94	1.49	1.9
Rayons gamma Co^{60} + Cystamine ...	2.94	2.42	1.2
Radiophosphore P^{32} + Cystamine	3.00	2.07	1.5

PATT et collaborateurs, étudiant l'action radioprotectrice de la cystéine (23), ont estimé le D. R. F. à environ 1.7. Dans leurs conditions d'expérience, cette valeur est indépendante de la dose. Plus récemment, l'école de LANGENDORFF gagnait l'impression que le D. R. F. de la cystéamine augmente avec des doses croissantes (11). Dans une récente

communication CATSCH a démontré qu'il n'y a pas de parallélisme entre les lignes de régression pour le groupe protégé et pour le groupe contrôle de souris irradiées (10). De l'ensemble de ses observations sur la protection conférée par la cystéamine et l'isothiuronium, il évalue le rapport des coefficients de régression respectifs à environ 1.7. Compte tenu des conditions expérimentales, la concordance avec notre valeur calculée est satisfaisante. Dans le cas de la cystamine administrée *per os* pendant 30 jours, à des souris DBA_1 ayant reçu une injection intrapéritonéale de P^{32}, nous avons trouvé (22):

D. L. 50/30 jours du groupe contrôle: 4.5 μc/gr (P^{32})
D. L. 50/30 jours du groupe cystamine: 6.1 μc/gr (P^{32})
Le rapport des coefficients de régression est: 1.5 (tableau 3).

L'interprétation biologique de ces paramètres est obscure, ils ne sont probablement pas opérationnels. La mort par radiation est la résultante de l'action de facteurs nombreux dont certains sont encore mal connus.

En étudiant leur nature, leur rôle individuel, et l'action spécifique sur chacun d'eux des agents protecteurs, nous pouvons espérer résoudre l'important problème de la radioprotection des êtres vivants.

RÉSUMÉ

L'action de la cystamine *per os* contre la mort par radiation a été étudié chez des souris irradiées par le Co^{60}. Au total, 355 souris C57B1/6, mâles et femelles, âgées de 38 ± 3 jours, ont été réparties dans des séries de traitement recevant quatre doses totales différentes selon une échelle progressive, délivrées en deux fractions égales à 5 jours d'intervalle. Les résultats sont analysés par la méthode des probits. Dans le groupe de souris traitées par la cystamine *per os*, la D. L. 50/30 jours est passé de 416 r à 597 r. Le degré de protection obtenu est significatif. Les lignes de régression se rapportant au groupe contrôle et au groupe traité par la cystamine forment un angle aigu ouvert à droite. Ce résultat est comparé à celui obtenu tant avec la cystéamine qu'avec la cystamine *per os* et le P^{32} administré par voie intrapéritonéale. Une interprétation de cette caractéristique commune est présentée, considérant que, dans nos conditions d'expérience, l'action létale des radiations ionisantes sur les mammifères, est statistiquement assimilable à l'action conjointe et indépendante de deux composantes. Le mécanisme d'action des radioprotecteurs chimiques est discuté en conséquence de même que certaines implications sur les valeurs du F. R. D. (facteur de réduction de dose).

SUMMARY

The action of cystamine *per os* against radiation death was investigated in mice irradiated with Co^{60}. A total of 355 C57B1/6 mice of both sexes, aged 38 ± 3 days was assigned to treatment groups receiving four different total doses according to a graded sequence, in two fractions at a 5-day interval. The data were analyzed by the probit method. In the group treated with cystamine *per os* the 30-day L. D. 50 value was increased from 416 r to 597 r. The degree of protection afforded was significant. The representative regression curves for control and cystamine groups formed a sharp angle

open towards the right side. Comparison is made with similar results obtained with cysteamine and also cystamine *per os* and intraperitoneal P^{32}. A possible explanation of this common pattern is presented, assuming that the killing action of ionizing radiations in mammals is statistically similar, under the experimental conditions, to the joint independent action of two components. The mechanism of action of protective chemical agents is discussed accordingly as well as implications on the D. R. F. values (dose reduction factor).

ZUSAMMENFASSUNG

Die Wirkungsweise des *per os* zugeführten Zystamines gegen Strahlentod wurde an Mäusen untersucht, die mit Co^{60} bestrahlt worden sind. Insgesamt 355 C57B1/6 Mäuse beiden Geschlechts, die 38 ± 3 Tage alt waren, sind auf verschiedene Behandlungsgruppen verteilt worden. Diese erhielten entsprechend einer gradierten Reihenfolge vier verschiedene Totaldosen in zwei gleichgrossen Fraktionen mit einem Intervall von 5 Tagen. Die Daten wurden mit Hilfe der Testmethode untersucht. In der mit Zystamin *per os* behandelten Gruppe stieg der L. D. 50-Wert von 416 r auf 597 r an. Der Grad des gebotenen Schutzes war signifikant. Die repräsentativen Regressionskurven für die Kontroll- und Zystamingruppen bildeten einen scharfen nach rechts offenen Winkel. Vergleiche mit ähnlichen Resultaten, die man mit Zysteamin und auch mit Zystamin *per os* und intraperitoneal appliziertem P^{32} erhalten hat, werden angestellt. Eine mögliche Erklärung dieses gewöhnlichen Musters wird vorgelegt, wobei man annimmt, dass der tödliche Effekt der jonisierenden Strahlung bei den Säugetieren unter experimentellen Bedingungen statistisch dem gemeinsamen unabhängigen Effekt zweier Komponenten ähnelt. Der Mechanismus der Wirkungsweise chemischer Schutzmittel sowie Einflüsse auf die Faktoren der Dosisverminderung werden diskutiert.

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CASE REPORTS

FROM THE ROENTGEN DEPARTMENT (DIRECTOR: H. GLADNIKOFF), SAMARITEN HOSPITAL FOR CHILDREN, STOCKHOLM, SWEDEN

CALCIFIED DISC PROTRUSION IN CHILDREN

by

I. Bjelkhagen and *H. Gladnikoff*

Nucleus pulposus calcifications are common in adult subjects (RATHKE) and may be permanent or only temporary (SANDSTRÖM). The calcification may perforate the annulus posteriorly and result in disc protrusion (JUNGHANNS and SCHMORL, KNUTSSON). The same condition has been observed in veterinary surgery; thus, in roentgen examinations of 33 mature dogs with 54 disc protrusions, OLSSON has demonstrated calcification of the nucleus inside the fibrous annulus in 17 diseased intervertebral discs, calcifications in the disc protrusions alone in 5 cases, and in 12 cases calcification of the nucleus in the disc as well as in the disc protrusion.

Calcification of the nucleus pulposus in children has previously been described in only 23 cases, the first in 1922 by CALVÉ and GALLAND. We have, in addition, a material of 3 cases. Out of this total of 26 children, a number had several calcified intervertebral discs (Diagram 1). In only one of the earlier known cases was a posterior protrusion of

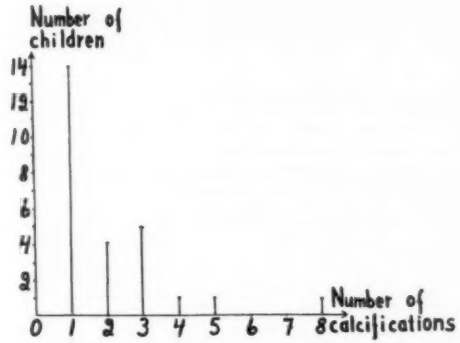

Diagram 1. Number of multiple calcifications.

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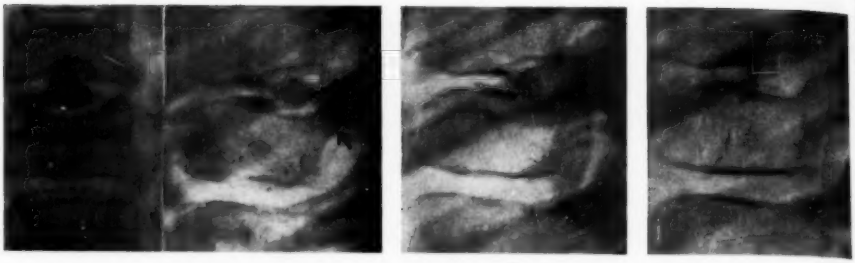

a b c

Fig. 1. Case 1. a) Three weeks after trauma: Calcification caudally to Th6, consisting of one ventral disc-shaped part, one middle egg-shaped part with indentations into adjacent portions of the Th6 and Th7, and one dorsal part forming a disc protrusion into spinal canal through posterior perforation of annulus. The disc is reduced in height. b) Two months after trauma: Posterior pole of calcification in middle extrudes into disc prolapse which has become fusiform and dissected its way posteriorly along vertebral body of Th7. c) Three months after trauma: Except for a few small grains pressed into disc protrusion, all calcification has disappeared. After 20 months: No calcification in intervertebral disc or in prolapse.

a calcified nucleus described (WEINGÄRTNER). The frequency of calcifications is probably greater, however, than may be deduced from the data reported in the literature; SILVERMAN found 7 cases during 5 years, after his attention had been drawn to these conditions, and our own three cases were encountered over a period of 3 years. In one of these latter there were calcifications in 8 discs; in the other two, disc protrusions were present.

Case 1. Female, aged 8 years, who fell and hit her back against some stairs; two weeks later she experienced pain in the back at nights and upon coughing or sneezing. Five weeks after the accident there was stiffness of the thoracic spine and tenderness over the spinous processes of the Th6 to Th8 vertebrae. There were no clinical signs of infection, nor of compression of the nerve roots nor of the spinal cord. *Roentgen examination* (Fig. 1): 3 weeks after the trauma: Calcified nucleus pulposus caudally to Th6. Two months after the trauma: The calcification was situated partly in a protrusion dorsally to the vertebral body of Th7. After 3 months: Practically all the calcifications were situated in the disc protrusion; after 20 months they had disappeared. Pain and stiffness subsided after 3 weeks rest from all gymnastics but the girl still had periods of weakness in her back 2 years after the accident.

Case 2. Male, aged 3 years, had had torticollis at the age of $1^1/_2$ years, pseudocroup twice, and recurrent traumata since starting to walk. The clinical examination showed slight torticollis but no impairment of movement. *Roentgen examination* (Fig. 2): Calcification of nucleus pulposus caudally from C2 to C5, at Th2, and from Th10 to Th12. The calcified nucleus of the disc caudally to C5 protruded partly through an anterior perforation of the annulus fibrosis. Six months later an increased part of the calcification was pressed out in the protrusion.

Case 3. Female, aged $3^1/_2$ years, with acute pain in the neck; no history of trauma, no fever, and no signs except torticollis with restricted mobility of the neck. *Roentgen examination:* Disc-shaped calcified nucleus pulposus between C2 and C3.

The calcifications are granulous, or show no structure at all, and accumulate in rounded or egg-shaped lumps; they may also be present as a more or less thick plate in the disc. Generally, the calcifications are situated in the posterior part of the disc, but may occasionally appear anteriorly; they are practically always in the midline but may sometimes involve almost the whole disc.

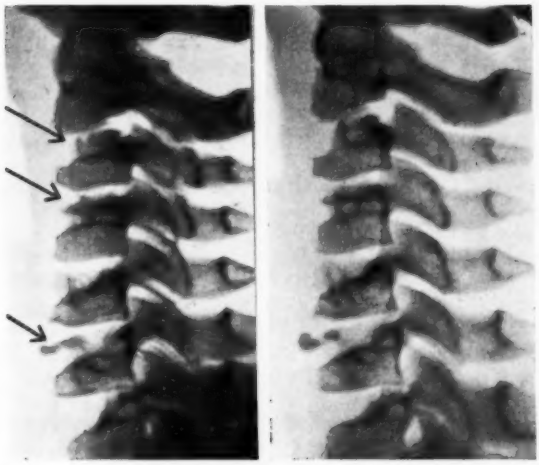

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Fig. 2. Case 2. a) Calcified nuclei in 8 intervertebral discs. Protrusion forwards of calcified nucleus between C5 and C6, and indentations in several vertebral bodies. b) Six months later: The herniated part of the disc has increased, and the opening in the annulus has caused a 'waist' to appear in the calcification.

In about two-thirds of the 26 cases discussed, impressions of the calcifications and surrounding cartilage (Fig. 3) were visible in adjacent parts of the vertebral bodies.

No nucleus calcifications have been described caudally to L2 in children (Fig. 3). They have thus another position than the common disc degeneration and the common disc protrusions in adults. Most frequently the lesions are only temporary in children. In one case a calcification disappeared after 2 weeks; they disappear generally within a year. In 4 of the 26 cases, calcifications, unaltered in size, were still present after a period of observation from between $3^1/_2$ to 10 years; these four cases therefore seem to be permanent.

The distribution with respect to different ages is fairly even. One child was less than one year old. Twelve were boys and 12 girls.

The etiology is unknown. Trauma with vascular damage, hematoma in the disc, or ischaemic necrosis, have been suggested as possible causes. Calcifications in children have, however, not been described in cases of disc lesions acquired in connection with fractures of the vertebral bodies. Nor does calcification appear as a consequence of operative enucleation of a disc herniation although the surgical defect in the disc often becomes filled with blood. No traumata were reported in 20 of the 26 cases and a traumatic genesis therefore seems improbable. Yet the possibility that trauma may have caused rupture of the annulus fibrosis in an already diseased disc in two of our cases cannot be excluded. That infection may have been the cause is less probable. Calcification has not been observed in cases of disc infection nor in cases of the undulant fever Bang, of typhus fever, or infection due to puncture. Alkoptonuria may cause calcifications in cartilage but not in children. Hypercalcaemia does not produce accumulation of calcium in the nucleus.

Symptoms and signs. These consist of pain with impairment of mobility, and eventually fever. In 5 of the 26 cases, however, the calcifications were secondary findings. In

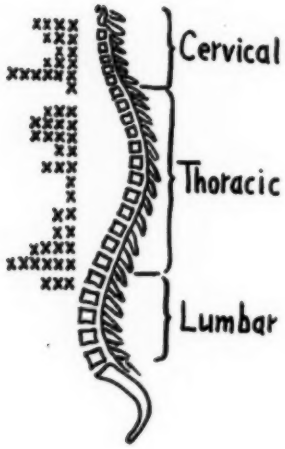

Fig. 3. Sites of nucleus calcifications in 26 cases (each × indicates one calcified nucleus).

our Case 2, there was only a slight torticollis. It may therefore be difficult in the individual cases to determine immediately, for instance, whether pain in the neck with torticollis may be due to the nucleus calcification demonstrated.

Treatment. In cases of symptom-free nucleus calcifications no treatment is required. In the other cases it is generally considered sufficient to prescribe rest and any suitable medication for the alleviating of pain and, eventually, shorter periods of immobilization.

Prognosis. In all probability the long-time prognosis is excellent.

SUMMARY

The authors report 3 cases of calcification of the nucleus pulposus in children, in two of which the calcification had penetrated the annulus fibrosis and resulted in disc protrusion. These, together with 23 cases of nucleus calcification earlier recorded in the literature, are analysed with respect to their sites in the spine, age, and sex distribution, as well as to duration and prognosis.

ZUSAMMENFASSUNG

Die Verfasser berichten 3 Fälle mit Verkalkung des Nucleus pulposus im Kindesalter. In 2 dieser Fälle hatte die Verkalkung den Annulus fibrosus penetriert und eine Protrusion der Zwischenwirbelscheibe ergeben. Zusammen mit 23 bisher in der Literatur registrierten Fällen mit Nucleusverkalkungen werden diese beiden Fälle in Bezug auf ihre Lage in der Wirbelsäule, die Alters- und Geschlechtsverteilung sowie auf die Duration und Prognose analysiert.

RÉSUMÉ

Les auteurs présentent 3 cas de calcification du nucléus pulposus chez des enfants; dans deux de ces cas la calcification avait traversé l'annulus fibrosus et donné une protrusion discale. Ils étudient ces cas, avec les 23 cas de calcification du nucléus déjà publiés dans la littérature, au point de vue du siège dans le rachis, de l'âge, de la répartition suivant le sexe, de la durée et du pronostic.

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FROM THE ROENTGEN DEPARTMENTS OF KAROLINSKA SJUKHUSET AND KRONPRINSESSAN LOVISAS BARNSJUKHUS, STOCKHOLM, SWEDEN

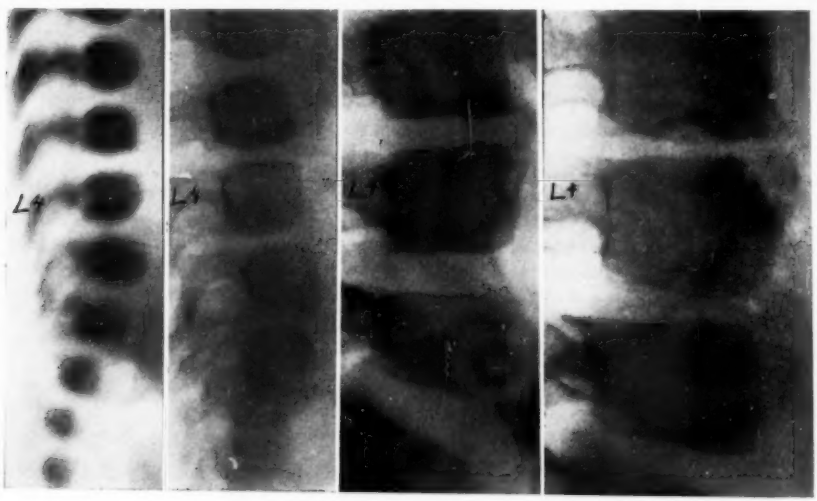
DISSECTING DISC HERNIATION IN A 4-YEAR-OLD CHILD

by

K. Ekengren and *K. Lindblom*

Intraspongious herniations of intervertebral discs are usually looked upon as findings without clinical signs. In many cases this is true also of their dissecting form, by some authors called a 'persisting epiphysis'.

Intraspongious herniations are usually found first in young adults. Regression of nutritive vessels to the intervertebral discs, taking place at 20 years of age, with secondary prolapse of disc tissue through the vessel canals has been presumed as one cause of intraspongious herniations (Übermuth, Böhmig, et al.), while a traumatic origin was pointed out by other authors (Schmorl & Junghanns). Recent observations in a series



a b c d

Fig. 1. Lateral films of spine at a) 1 day, b) 5 months, c) 4 years, and d) 8 years of age demonstrating development of dissecting disc herniation (c—d) in the upper surface of L4 with lowering of adjacent disc and formation of osteophyte at L3.

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of injuries during childhood (RENCK & SCHELLER) and experimental work on anatomic specimens (KEYES & COMPERE, PEREY) are in favour of these herniations being traumatic.

Though no injury was known in the case described below the early appearance of a dissecting disc herniation does not agree with the theory of prolapse through vascular canals. In addition, it is the first observation described of this lesion in early childhood.

The child was a girl born on 9 August 1948 with anal atresia and a recto-vaginal fistula and was later operated upon with reconstruction of the anus. She was examined several times during the years 1948—1956 because of faecal impaction. No history of back symptoms, spondylitis, or trauma was present.

On roentgen examination at birth a wedge deformity was found of the 10th vertebra combined with costal fusions on both sides and considered to be a congenital malformation. Neither at birth nor at two years of age was anything abnormal seen in the fourth lumbar vertebra. When the child was four, a small fragment of the anterior margin of the fourth lumbar vertebra was found to be separated and the adjacent disc appeared somewhat narrowed. During the following years up to the age of eight this separation grew more pronounced, the vertebra became larger in an anterior direction and the adjacent disc definitely narrowed; in addition, there was an osteophyte at the lower margin of L3. (Figs. 1 and 2.) No tenderness or pain was present at a recent examination.

The whole course in the fourth lumbar vertebra was similar to that of a dissecting transosseous rupture of an intervertebral disc (LINDBLOM). Whether this caused abdominal pain or not could not be determined because of the painful attacks of recurrent faecal impactions from which the patient suffered.

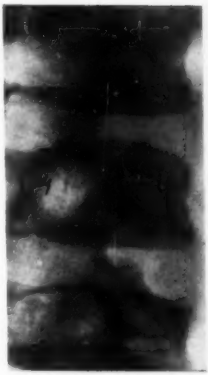

Fig. 2. Oblique film of spine obtained at same time as fig. 1 c illustrating that separation of anterior fragment from L4 does not extend to lateral side of vertebral body.

SUMMARY

A case is described of a dissecting disc herniation in the fourth lumbar vertebra; this appeared at four years of age with progressive changes which were watched for four years.

ZUSAMMENFASSUNG

Ein fall mit dissekierendem Zwischenwirbelscheibenbruch in den 4. Lendenwirbel wird beschrieben. Dieser trat im Alter von vier Jahren auf und zeigte progressive Veränderungen, die 4 Jahre lang beobachtet wurden.

RÉSUMÉ

Description d'un cas de hernie discale disséquante de la quatrième vertèbre lombaire, apparue à l'âge de quatre ans; la progression des lésions a été observée pendant quatre ans.

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A CASE OF THORACIC INTERVERTEBRAL DISC PROTRUSION

by

Folke Knutsson

Disc herniation in the thoracic spine is rare. The first case diagnosed clinically and roentgenologically and treated by operation was described by ANTONI (1931). LOVE and KIEFER (1950) have published a series of 17 cases, and MÜLLER (1950) a series of 4.

The clinical picture varies greatly according to the site and degree of the lesion. Common features are radiating pain and varying degrees of paraplegia, according to the extent of compression of the pyramidal tracts.

The case described is of a woman of 50 years. In April 1953 she experienced a period of lumbago-like pains between the shoulderblades, radiating round the chest. Pleurisy was suspected, and roentgen examination of the chest carried out. In the lateral view a homogeneous calcified area the size of a pea was seen in the middle of the disc between Th 7 and 8.

The patient was treated in hospital in February and March 1956 for kidney disease, during which period she experienced rapidly developing diminished sensitivity of both legs, but no signs of a pyramidal tract lesion. Roentgen examination of the thoracic spine now revealed posterior prolapse of the calcified disc, part of the disc substance lying on the posterior surface of the body of Th 7. Oxygen myelography was undertaken to ascertain whether this prolapse was causing pressure on the spinal cord. No such effect was found, and the prolapsed disc was assumed to be situated under the posterior longitudinal ligament.

No clinical explanation of the impairment of sensitivity has been found.

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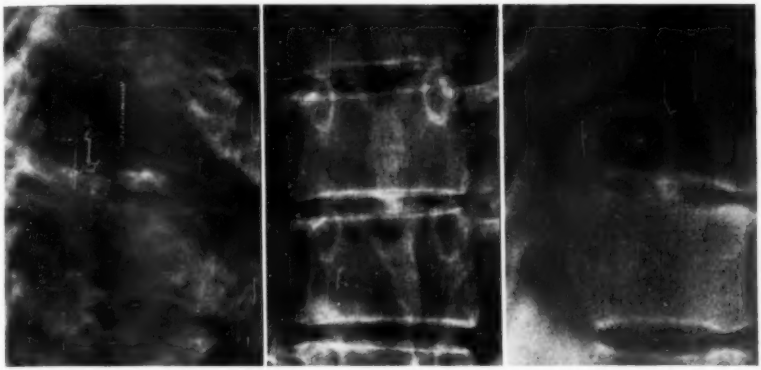

a b c

Fig. 1. a) Lateral view of chest, showing area of calcification the size of a pea at the centre of the disc between Th 7 and 8. b) and c) Examination 3 years later reveals prolapse of part of the disc substance, which is now lying on the posterior surface of the body of Th 7.

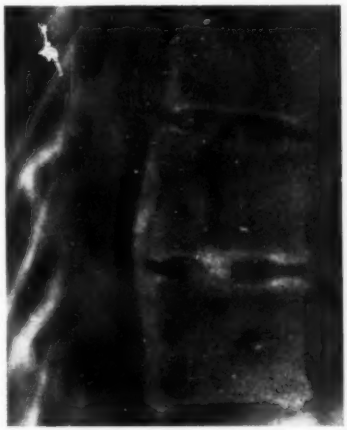

Fig. 2. Oxygen myelography. Tomography reveals that the subarachnoid space is unaffected, and that the prolapse is causing no pressure on cord. The prolapsed disc substance is probably lying under the posterior longitudinal ligament.

The case illustrates that a considerable median disc prolapse may be present without causing pressure on the cord. The degree of protrusion can be assessed only with the aid of myelography.

SUMMARY

A case of degeneration of a thoracic intervertebral disc with central calcification is described. Myelography showed that the prolapsed disc was not causing pressure on the cord, but was probably lying under the posterior longitudinal ligament. A roentgenogram taken 3 years earlier showed the area of calcification but no prolapse.

ZUSAMMENFASSUNG

Ein Fall mit Degeneration einer thorakalen Zwischenwirbelscheibe mit zentraler Verkalkung wird beschrieben. Eine Myelographie zeigte, dass der prolabierte Diskus keinen Druck auf das Rückenmark ausübte, aber dass er wahrscheinlich unter dem Ligamentum longitudinale posterior lag. Eine drei Jahre vorher gemachte Röntgenaufnahme zeigte das Gebiet der Verkalkung, aber keinen Prolaps.

RÉSUMÉ

L'auteur présente un cas de dégénérescence d'un disque intervertébral dorsal avec calcification centrale. La myélographie a montré que le disque prolabé ne comprimait pas la moëlle, mais qu'il était probablement situé sous le ligament longitudinal postérieur. Une radiographie prise 3 ans plus tôt montrait l'aire calcifiée, mais pas de prolapsus.

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